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Quantum and Cancer Biology Research Literatures

Dr. Mark Herbert

World Development Institute
39-06 Main Street, Flushing, Queens, New York 11354, USA, ma708090@gmail.com

Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This article introduces recent research reports as references in the related studies.
[Herbert M. **Quantum and Cancer Biology Research Literatures.**Cancer Biology 2022;12(3):8-146]. ISSN: 2150-1041 (print); ISSN: 2150-105X (online). http://www.cancerbio.net 02.doi:10.7537/marscbj120322.02.

Key words: cancer; life; research; literature; cell

1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

A, R., et al. (2017). "Synthesis and evaluation of the cytotoxic and anti-proliferative properties of ZnO quantum dots against MCF-7 and MDA-MB-231 human breast cancer cells." Mater Sci Eng C Mater Biol Appl **81**: 551-560.

Current trends in therapeutic research are the application of nanomaterial carriers for cancer therapy. One such molecule, ZnO, originally used in diagnosis and as a drug carrier, is gaining importance for its biological properties. Here, we report for the first time, the scope of ZnO QDs for enhanced cytotoxicity against MCF-7 and metastatic MDA-MB-231 human breast cancer cells. Unlike other ZnO nanostructures, ZnO QDs are dispersed and small sized (8-10nm) which is believed to greatly increase the cellular uptake. Furthermore, the acidic tumor microenvironment attracts ZnO QDs enhancing targeted therapy while leaving normal cells less affected. Results from MTT assay demonstrated that ZnO QDs induced cytotoxicity to MCF-7 and metastatic MDA-MB-231 breast cancer cells at very low concentrations (10 and 15mug/ml) as compared to other reported ZnO nanostructures. HEK-293 cells showed less toxicity at these concentrations. Confocal microscope images from DAPI staining and TUNEL assay demonstrated that ZnO QDs induced nuclear fragmentation and apoptosis in MCF-7 and MDA-MB-231. FACS results suggested ZnO QDs treatment induced cell cycle arrest at the G0/G1 phase in these cells. ZnO QDs drastically decreased the proliferation and migration of MCF-7 and MDA-MB-231 as seen from the results of the clonogenic and wound healing assays respectively. Furthermore, our data suggested that ZnO QDs regulated apoptosis via Bax and Bcl-2 proteins as validated by immunofluorescence and western blot. Taken together, our findings demonstrate that these ultra-small sized ZnO QDs destabilize cancer cells by using its acidic tumor microenvironment thereby inducing apoptosis and controlling the cell proliferation and migration at low dosages.

AbdElhamid, A. S., et al. (2018). "Layer-by-layer gelatin/chondroitin quantum dots-based nanotheranostics: combined rapamycin/celecoxib delivery and cancer imaging." Nanomedicine (Lond) **13**(14): 1707-1730.

Aim: Nanotheranostics consisting of highly-fluorescent quantum dots coupled with gelatin/chondroitin layer-by-layer assembled nanocapsules were developed. Materials & methods: The hydrophobic drugs celecoxib (CXB) and rapamycin (RAP) were co-loaded into the oily core of nanocapsules (NCs) to enable synergistic growth inhibition of breast cancer cells. To overcome the nonspecific binding of actively targeted CS-NCs with normal cells, a matrix metalloproteinase (MMP-2)-degradable cationic gelatin layer was electrostatically deposited onto the surface of the negatively-charged CS-NCs. Results: The prepared

nanocarriers displayed strong fluorescence which enabled tracing their internalization into cancer cells. An enhanced cytotoxicity of the NCs against breast cancer cells was demonstrated. In vivo, the nanoplatforms displayed superior antitumor efficacy as well as nonimmunogenic response. Conclusion: Therefore, these multifunctional nanoplatforms could be used as potential cancer theranostics.

AbdElhamid, A. S., et al. (2018). "Lactoferrin-tagged quantum dots-based theranostic nanocapsules for combined COX-2 inhibitor/herbal therapy of breast cancer." Nanomedicine (Lond) **13**(20): 2637-2656.

AIM: Herein, tumor-targeted quantum dots (QDs)-based theranostic nanocapsules (NCs) coloaded with celecoxib and honokiol were developed. Materials & methodology: The anionic CD44-targeting chondroitin sulfate and cationic low density lipoprotein (LDL)-targeting lactoferrin (LF) were sequentially assembled onto the surface of the positively charged oily core. As an imaging probe, highly fluorescent mercaptopropionic acid-capped cadmium telluride QDs were coupled to LF. RESULTS: In vitro, fluorescence of QDs was quenched (OFF state) due to combined electron/energy transfer-mediated processes involving LF. After intracellular uptake of NCs, fluorescence was restored (ON state), thus enabled tracing their internalization. The NCs demonstrated enhanced cytotoxicity against breast cancer cells as well as superior in vivo antitumor efficacy. CONCLUSION: We propose these multifunctional nanotheranostics for imaging and targeted therapy of breast cancer.

Ahmad, J., et al. (2015). "Zinc oxide quantum dots: a potential candidate to detain liver cancer cells." Bioprocess Biosyst Eng **38**(1): 155-163.

The term cancer is used for diseases in which abnormal cells proliferate without control and are able to attack with other tissues. Over various types of cancers, liver cancer is the most hurtful disease, which affects the whole body system. The aim of the present study was to investigate the efficiency against cancer cells of HepG2 cells, with quantum dots of ZnO. The cytotoxic effects were analyzed with MTT assays in range of 1-100 mug/ml. The cells were exposed to ZnO-QDs and it exhibit significant reduction, which starts from concentration 5 mug/ml (4 %; $p < 0.05$). The assay was justified with quantitative RT-PCR and it demonstrates, exposure of ZnO-QDs on HepG2 cells. The level of mRNA expressions was significantly up-regulated (Bax, P53, and Caspase-3), whereas the anti-apoptotic gene (Bcl-2) was down-regulated. The QDs (5 +/- 2 nm) were prepared via soft chemical solution process and analyzed using FESEM, TEM and HR-TEM.

Ajgaonkar, R., et al. (2022). "Detection of Pancreatic Cancer miRNA with Biocompatible Nitrogen-Doped Graphene Quantum Dots." Materials (Basel) **15**(16).

Early-stage pancreatic cancer remains challenging to detect, leading to a poor five-year patient survival rate. This obstacle necessitates the development of early detection approaches based on novel technologies and materials. In this work, the presence of a specific pancreatic cancer-derived miRNA (pre-miR-132) is detected using the fluorescence properties of biocompatible nitrogen-doped graphene quantum dots (NGQDs) synthesized using a bottom-up approach from a single glucosamine precursor. The sensor platform is comprised of slightly positively charged (1.14 +/- 0.36 mV) NGQDs bound via pi-pi stacking and/or electrostatic interactions to the negatively charged (-22.4 +/- 6.00 mV) bait ssDNA; together, they form a complex with a 20 nm average size. The NGQDs' fluorescence distinguishes specific single-stranded DNA sequences due to bait-target complementarity, discriminating them from random control sequences with sensitivity in the micromolar range. Furthermore, this targetability can also detect the stem and loop portions of pre-miR-132, adding to the practicality of the biosensor. This non-invasive approach allows cancer-specific miRNA detection to facilitate early diagnosis of various forms of cancer.

Akinfieva, O., et al. (2013). "New directions in quantum dot-based cytometry detection of cancer serum markers and tumor cells." Crit Rev Oncol Hematol **86**(1): 1-14.

The use of fluorescent quantum dots (QDs) incorporated in or tagged with polymeric microbeads allows multiplexed coding of biomolecules. Compared to organic dyes, QDs are characterized by improved imaging capabilities, brightness, and photostability and may be used for simultaneous detection of multiple biomarkers. Development of QD conjugates and QD-encoded suspension arrays has given rise to new promising approaches to cell labeling, in vivo visualization, and diagnostic assay techniques. QDs have proved to be efficient donors for Forster resonance energy transfer (FRET) and are characterized by high multiphoton absorption coefficients. Implication of QD-based suspension arrays for identification of autoantibodies, tumor-specific T cells, and detection of circulating cancer cells by means of flow cytometry, holds considerable promise for earliest diagnosis of human abnormalities and effective monitoring of the therapeutic effects. This review summarizes recent advances in QD-based suspension arrays application to cancer diagnosis and attempts to predict their diagnostic potential in a future.

Al Dine, E. J., et al. (2018). "A Facile Approach for Doxorubicine Delivery in Cancer Cells by Responsive

and Fluorescent Core/Shell Quantum Dots." Bioconjug Chem **29**(7): 2248-2256.

Biocompatible thermoresponsive copolymers based on 2-(2-methoxyethoxy) ethyl methacrylate (MEO2MA) and oligo (ethylene glycol) methacrylate (OEGMA) were grown from the surface of ZnO quantum dots (QDs) by surface initiated atom transfer radical polymerization with activators regenerated by electron transfer (SI-ARGET ATRP) in order to design smart and fluorescent core/shell nanosystems to be used toward cancer cells. Tunable lower critical solution temperature (LCST) values were obtained and studied in water and in culture medium. The complete efficiency of the process was demonstrated by the combination of spectroscopic and microscopic studies. The colloidal behavior of the ZnO/copolymer core/shell QDs in water and in physiological media with temperature was assessed. Finally, the cytotoxicity toward human colon cancer HT29 cells of the core/shell QDs was tested. The results showed that the polymer-capped QDs exhibited almost no toxicity at concentrations up to 12.5 mug.mL(-1), while when loaded with doxorubicin hydrochloride (DOX), a higher cytotoxicity and a decreased HT29 cancer cell viability in a short time were observed.

Aldughaim, M. S., et al. (2021). "Gene Expression and Transcriptome Profiling of Changes in a Cancer Cell Line Post-Exposure to Cadmium Telluride Quantum Dots: Possible Implications in Oncogenesis." Dose Response **19**(2): 15593258211019880.

Cadmium telluride quantum dots (CdTe-QDs) are acquiring great interest in terms of their applications in biomedical sciences. Despite earlier sporadic studies on possible oncogenic roles and anticancer properties of CdTe-QDs, there is limited information regarding the oncogenic potential of CdTe-QDs in cancer progression. Here, we investigated the oncogenic effects of CdTe-QDs on the gene expression profiles of Chang cancer cells. Chang cancer cells were treated with 2 different doses of CdTe-QDs (10 and 25 mug/ml) at different time intervals (6, 12, and 24 h). Functional annotations helped identify the gene expression profile in terms of its biological process, canonical pathways, and gene interaction networks activated. It was found that the gene expression profiles varied in a time and dose-dependent manner. Validation of transcriptional changes of several genes through quantitative PCR showed that several genes upregulated by CdTe-QD exposure were somewhat linked with oncogenesis. CdTe-QD-triggered functional pathways that appear to associate with gene expression, cell proliferation, migration, adhesion, cell-cycle progression, signal transduction, and metabolism. Overall, CdTe-QD exposure led to changes in the gene expression profiles of the Chang cancer cells, highlighting that this nanoparticle can further drive oncogenesis and cancer progression, a finding that indicates the merit of immediate in vivo investigation.

Al-Jamal, W. T., et al. (2008). "Functionalized-quantum-dot-liposome hybrids as multimodal nanoparticles for cancer." Small **4**(9): 1406-1415.

Functionalized-quantum-dot-liposome (f-QD-L) hybrid nanoparticles are engineered by encapsulating poly(ethylene glycol)-coated QD in the internal aqueous phase of different lipid bilayer vesicles. f-QD-L maintain the QD fluorescence characteristics as confirmed by fluorescence spectroscopy, agarose gel electrophoresis, and confocal laser scanning microscopy. Cationic f-QD-L hybrids lead to dramatic improvements in cellular binding and internalization in tumor-cell monolayer cultures. Deeper penetration into three-dimensional multicellular spheroids is obtained for f-QD-L by modifying the lipid bilayer characteristics of the hybrid system. f-QD-L are injected intratumorally into solid tumor models leading to extensive fluorescent staining of tumor cells compared to injections of the f-QD alone. f-QD-L hybrid nanoparticles constitute a versatile tool for very efficient labeling of cells ex vivo and in vivo, particularly when long-term imaging and tracking of cells is sought. Moreover, f-QD-L offer many opportunities for the development of combinatory therapeutic and imaging (theranostic) modalities by incorporating both drug molecules and QD within the different compartments of a single vesicle.

Al-Ogaidi, I., et al. (2014). "Detection of the ovarian cancer biomarker CA-125 using chemiluminescence resonance energy transfer to graphene quantum dots." Chem Commun (Camb) **50**(11): 1344-1346.

An immunoassay has been developed for the detection of the ovarian cancer biomarker CA-125 by utilizing the chemiluminescence resonance energy transfer to graphene quantum dots. This biosensor shows a wide linear range from 0.1 U mL(-1) to 600 U mL(-1) with a limit of detection of 0.05 U mL(-1) for CA-125 in a buffer solution.

Amaral, J. L., et al. (2020). "Quantum biochemistry in cancer immunotherapy: New insights about CTLA-4/ipilimumab and design of ipilimumab-derived peptides with high potential in cancer treatment." Mol Immunol **127**: 203-211.

Cancer is a group of diseases involving disordered growth of abnormal cells with the potential to invade and spread to other parts of the body. Today, immunotherapy is the most efficient treatment, with fewer side effects. Notably, the employment of monoclonal antibodies to inhibit checkpoint proteins, such as CTLA-4, has caused much excitement among cancer immunotherapy researchers. Thus, in-depth

analysis through quantum biochemistry and molecular dynamics simulations was performed to understand the complex formed by ipilimumab and its target CTLA-4. Our computational results provide a better understanding of the binding mechanisms and new insights about the CTLA-4: ipilimumab interaction, identifying essential amino acid residues to support the complex. Additionally, we report new interactions such as aromatic-aromatic, aromatic-sulfur, and cation-pi interactions to stabilize the CTLA-4:ipilimumab complex. Finally, quantum biochemistry analyses reveal the most important amino acid residues involved in the CTLA-4:ipilimumab interface, which were used to design synthetic peptides to inhibit CTLA-4. The computational results presented here provide a better understanding of the CTLA-4:ipilimumab binding mechanisms, and can support the development of alternative antibody-based drugs with high relevance in cancer immunotherapy.

Amin, J., et al. (2022). "Breast microscopic cancer segmentation and classification using unique 4-qubit-quantum model." Microsc Res Tech **85**(5): 1926-1936.

The visual inspection of histopathological samples is the benchmark for detecting breast cancer, but a strenuous and complicated process takes a long time of the pathologist practice. Deep learning models have shown excellent outcomes in clinical diagnosis and image processing and advances in various fields, including drug development, frequency simulation, and optimization techniques. However, the resemblance of histopathologic images of breast cancer and the inclusion of stable and infected tissues in different areas make detecting and classifying tumors on entire slide images more difficult. In breast cancer, a correct diagnosis is needed for complete care in a limited amount of time. An effective detection can relieve the pathologist's workload and mitigate diagnostic subjectivity. Therefore, this research work investigates improved the pre-trained xception and deeplabv3+ design semantic model. The model has been trained on input images with ground masks on the tuned parameters that significantly improve the segmentation of ultrasound breast images into respective classes, that is, benign/malignant. The segmentation model delivered an accuracy of greater than 99% to prove the model's effectiveness. The segmented images and histopathological breast images are transferred to the 4-qubit-quantum circuit with six-layered architecture to detect breast malignancy. The proposed framework achieved remarkable performance as contrasted to currently published methodologies. HIGHLIGHTS: This research proposed hybrid semantic model using pre-trained xception and deeplabv3 for breast microscopic cancer classification in to benign and malignant classes at accuracy of 95% accuracy, 99% accuracy for detection of breast malignancy.

Andrade, C. G., et al. (2013). "Evaluation of glycophenotype in breast cancer by quantum dot-lectin histochemistry." Int J Nanomedicine **8**: 4623-4629.

Cell surface glycoconjugates play an important role in differentiation/dedifferentiation processes and lectins are employed to evaluate them by several methodologies. Fluorescent probes are considered a valuable tool because of their ability to provide a particular view, and are more detailed and sensitive in terms of cell structure and molecular content. The aim of this study was to evaluate and compare the expression and distribution of glycoconjugates in normal human breast tissue, and benign (fibroadenoma), and malignantly transformed (invasive ductal carcinoma) breast tissues. For this, we used mercaptosuccinic acid-coated Cadmium Telluride (CdTe) quantum dots (QDs) conjugated with concanavalin A (Con A) or Ulex europaeus agglutinin I (UEA I) lectins to detect alpha-D-glucose/mannose and L-fucose residues, respectively. The QD-lectin conjugates were evaluated by hemagglutination activity tests and carbohydrate inhibition assays, and were found to remain functional, keeping their fluorescent properties and carbohydrate recognition ability. Fluorescence images showed that different regions of breast tissue expressed particular types of carbohydrates. While the stroma was preferentially and intensely stained by QD-Con A, ductal cells were preferentially labeled by QD-UEA I. These results indicate that QD-lectin conjugates can be used as molecular probes and can help to elucidate the glycoconjugate profile in biological processes.

Asadi, P., et al. (2017). "Quantum mechanical/molecular mechanical and docking study of the novel analogues based on hybridization of common pharmacophores as potential anti-breast cancer agents." Res Pharm Sci **12**(3): 233-240.

In an attempt to identify some new potential leads as anti-breast cancer agents, novel hybrid compounds were designed by molecular hybridization approach. These derivatives were structurally derived from hybrid benzofuran-imidazole and quinazolinone derivatives, which had shown good cytotoxicity against the breast cancer cell line (MCF-7). Since aromatase enzyme (CYP19) is highly expressed in the MCF-7 cell line, the binding of these novel hybrid compounds to aromatase was investigated using the docking method. In this study, due to the positive charge on the imidazole ring of the designed ligands and also, the presence of heme iron in the active site of the enzyme, it was decided to optimize the ligand inside the protein to obtain more realistic atomic charges for it. Quantum mechanical/molecular mechanical (QM/MM) method

was used to obtain more accurate atomic charges of ligand for docking calculations by considering the polarization effects of CYP19 on ligands. It was observed that the refitted charge improved the binding energy of the docked compounds. Also, the results showed that these novel hybrid compounds were adopted properly within the aromatase binding site, thereby suggesting that they could be potential inhibitors of aromatase. The main binding modes in these complexes were through hydrophobic and H bond interactions showing agreement with the basic physicochemical features of known anti aromatase compounds. Finally, the complex structures obtained from the docking study were used for single point QM/MM calculations to obtain more accurate electronic interaction energy, considering the electronic polarization of the ligand by its protein environment.

Atmaja, B., et al. (2010). "Targeting of Cancer Cells Using Quantum Dot-Polypeptide Hybrid Assemblies that Function as Molecular Imaging Agents and Carrier Systems." Adv Funct Mater **20**(23): 4091-4097.

We report a highly tunable quantum dot (QD)-polypeptide hybrid assembly system with potential uses for both molecular imaging and delivery of biomolecular cargo to cancer cells. In this work, we demonstrate the tunability of the assembly system, its application for imaging cancer cells, and its ability to carry a biomolecule. The assemblies are formed through the self-assembly of carboxyl-functionalized QDs and poly(diethylene glycol-L-lysine)-poly(L-lysine) (PEGLL-PLL) diblock copolypeptide molecules, and they are modified with peptide ligands containing a cyclic arginine-glycine-aspartate [c(RGD)] motif that has affinity for alphavbeta3 and alphavbeta5 integrins overexpressed on the tumor vasculature. To illustrate the tunability of the QD-polypeptide assembly system, we show that binding to U87MG glioblastoma cells can be modulated and optimized by changing either the conditions under which the assemblies are formed or the relative lengths of the PEGLL and PLL blocks in the PEGLL-PLL molecules. The optimized c(RGD)-modified assemblies bind integrin receptors on U87MG cells and are endocytosed, as demonstrated by flow cytometry and live-cell imaging. Binding specificity is confirmed by competition with an excess of free c(RGD) peptide. Finally, we show that the QD-polypeptide assemblies can be loaded with fluorescently labeled ovalbumin, as a proof-of-concept for their potential use in biomolecule delivery.

Au, G. H., et al. (2012). "Assessing breast cancer margins ex vivo using aqueous quantum-dot-molecular probes." Int J Surg Oncol **2012**: 861257.

Positive margins have been a critical issue that hinders the success of breast- conserving surgery. The incidence of positive margins is estimated to range from 20% to as high as 60%. Currently, there is no effective intraoperative method for margin assessment. It would be desirable if there is a rapid and reliable breast cancer margin assessment tool in the operating room so that further surgery can be continued if necessary to reduce re-excision rate. In this study, we seek to develop a sensitive and specific molecular probe to help surgeons assess if the surgical margin is clean. The molecular probe consists of the unique aqueous quantum dots developed in our laboratory conjugated with antibodies specific to breast cancer markers such as Tn-antigen. Excised tumors from tumor-bearing nude mice were used to demonstrate the method. AQD-Tn mAb probe proved to be sensitive and specific to identify cancer area quantitatively without being affected by the heterogeneity of the tissue. The integrity of the surgical specimen was not affected by the AQD treatment. Furthermore, AQD-Tn mAb method could determine margin status within 30 minutes of tumor excision, indicating its potential as an accurate intraoperative margin assessment method.

Awad, N. S., et al. (2021). "Ultrasound-Triggered Liposomes Encapsulating Quantum Dots as Safe Fluorescent Markers for Colorectal Cancer." Pharmaceutics **13**(12).

Quantum dots (QDs) are a promising tool to detect and monitor tumors. However, their small size allows them to accumulate in large quantities inside the healthy cells (in addition to the tumor cells), which increases their toxicity. In this study, we synthesized stealth liposomes encapsulating hydrophilic graphene quantum dots and triggered their release with ultrasound with the goal of developing a safer and well-controlled modality to deliver fluorescent markers to tumors. Our results confirmed the successful encapsulation of the QDs inside the core of the liposomes and showed no effect on the size or stability of the prepared liposomes. Our results also showed that low-frequency ultrasound is an effective method to release QDs encapsulated inside the liposomes in a spatially and temporally controlled manner to ensure the effective delivery of QDs to tumors while reducing their systemic toxicity.

Azevedo, V., et al. (2022). "Quantum transfer learning for breast cancer detection." Quantum Mach Intell **4**(1): 5.

One of the areas with the potential to be explored in quantum computing (QC) is machine learning (ML), giving rise to quantum machine learning (QML). In an era when there is so much data, ML may benefit from either speed, complexity or smaller amounts of storage. In this work, we explore a quantum approach to a machine learning problem. Based on the work of Mari et al., we train a set of hybrid classical-

quantum neural networks using transfer learning (TL). Our task was to solve the problem of classifying full-image mammograms into malignant and benign, provided by BCDR. Throughout the course of our work, heatmaps were used to highlight the parts of the mammograms that were being targeted by the networks while evaluating different performance metrics. Our work shows that this method may hold benefits regarding the generalization of complex data; however, further tests are needed. We also show that, depending on the task, some architectures perform better than others. Nonetheless, our results were superior to those reported in the state-of-the-art (accuracy of 84% against 76.9%, respectively). In addition, experiments were conducted in a real quantum device, and results were compared with the classical and simulator.

Azizi, M., et al. (2020). "Synthesis of Self-Targeted Carbon Dot with Ultrahigh Quantum Yield for Detection and Therapy of Cancer." ACS Omega **5**(38): 24628-24638.

This study aims to engineer a new type of ultrahigh quantum yield carbon dots (CDs) from methotrexate (MTX-CDs) with self-targeting, imaging, and therapeutic effects on MDA-MB 231 breast cancer cells. CDs were synthesized via a straightforward thermal method using a methotrexate (MTX) drug source. The physicochemical characteristics of the prepared MTX-CDs were studied using Fourier transform infrared (FT-IR) spectroscopy, transmission electron microscopy (TEM), dynamic light scattering (DLS), X-ray powder diffraction (XRD), and X-ray photoelectron spectroscopy (XPS). TEM and DLS revealed which MTX-CDs have homogeneous spherical morphology with a smaller average size of 5.4 +/- 2.2 nm, polydispersity index (PDI) of 0.533, and positive surface charge of around +3.93 mV. Results of FT-IR spectroscopy and high-resolution XPS indicated the presence of residues of MTX on CDs. Therefore, the synthesized MTX-CDs could be targeted and be taken up by FR-positive cell lines without the aid of additional targeting molecules. In vitro epifluorescence images demonstrated high-contrast cytoplasm biodistribution of MTX-CDs after 2 h of treatment. A much stronger fluorescent signal was detected in MDA-MB 231 compared to MCF 7, indicating their ability to precisely target FR. The highest cytotoxic and apoptotic effects were observed in MTX-CDs compared to free MTX obtained by the MTT assay, cell cycle arrest, and annexin V-FITC apoptosis techniques. Results revealed that the novel engineered MTX-CDs were capable of inducing apoptosis (70.2% apoptosis) at a lower concentration (3.2 muM) compared to free MTX, which was proved by annexin V and cell cycle. This work highlights the potential application of CDs for constructing an intelligent nanomedicine with integration of diagnostic, targeting, and therapeutic functions.

Babu, L. T. and P. Paira (2017). "Current Application of Quantum Dots (QD) in Cancer Therapy: A Review." Mini Rev Med Chem **17**(14): 1406-1415.

BACKGROUND & OBJECTIVE: Semiconductor quantum dots proved themselves as efficient fluorescent probes in cancer detection and treatment. Their size, high stability, non-photobleaching and water solubility made them a unique fluorophore in place of conventional organic dyes. METHOD: Newly emerged theranostic drug delivery system using quantum dots helped us in better understanding of the drug delivery mechanism inside the cells. Surface modified Quantum dots and their applications became wide in bioimaging, immunohistochemistry, tracking intracellular drug and intracellular molecules target. CONCLUSION: We have highlighted various applications of quantum dots in cancer treatment, drug delivery, flow cytometry, and theranostics.

Bae, P. K. and B. H. Chung (2014). "Multiplexed detection of various breast cancer cells by perfluorocarbon/quantum dot nanoemulsions conjugated with antibodies." Nano Converg **1**(1): 23.

The effective targeting of cancer cell surface antigens is an attractive approach in cancer diagnosis and therapy. Multifunctional nanoprobes with cell-targeting specificity are likely to find important applications in bioanalysis, biomedicine, and clinical diagnosis. In this study, we have fabricated biocompatible perfluorocan/quantum dot nanoemulsions as bimodal imaging nanoprobes for the targeting of breast cancer cells. Perfluorocarbon/quantum dot nanoemulsions conjugated with monoclonal antibodies, as a type of bimodal imaging nanoprobe based on (19) F-MR and optical imaging, have been synthesized and applied for targeted imaging of three different breast cancer cells (SKBR3, MCF-7, MDA-MB 468), respectively. We have shown that the cancer-detection capabilities of antibody-conjugated PFC/QDs nanoemulsions could be successfully applied to target of various breast cancer cells. These modified PFC/QDs nanoemulsions were shown to target the cancer cell surface receptors specially. Conjugation of ligands to nanoemulsions targeting over-expressed cell surface receptors is a promising approach for targeted imaging to tumor cells. We further propose that the PFC/QDs nanoemulsions could be used in targeted imaging of breast cancer cells.

Bagalkot, V., et al. (2007). "Quantum dot-aptamer conjugates for synchronous cancer imaging, therapy, and sensing of drug delivery based on bi-fluorescence

resonance energy transfer." Nano Lett **7**(10): 3065-3070.

We report a novel quantum dot (QD)-aptamer(Apt)-doxorubicin (Dox) conjugate [QD-Apt(Dox)] as a targeted cancer imaging, therapy, and sensing system. By functionalizing the surface of fluorescent QD with the A10 RNA aptamer, which recognizes the extracellular domain of the prostate specific membrane antigen (PSMA), we developed a targeted QD imaging system (QD-Apt) that is capable of differential uptake and imaging of prostate cancer cells that express the PSMA protein. The intercalation of Dox, a widely used antineoplastic anthracycline drug with fluorescent properties, in the double-stranded stem of the A10 aptamer results in a targeted QD-Apt(Dox) conjugate with reversible self-quenching properties based on a Bi-FRET mechanism. A donor-acceptor model fluorescence resonance energy transfer (FRET) between QD and Dox and a donor-quencher model FRET between Dox and aptamer result when Dox intercalated within the A10 aptamer. This simple multifunctional nanoparticle system can deliver Dox to the targeted prostate cancer cells and sense the delivery of Dox by activating the fluorescence of QD, which concurrently images the cancer cells. We demonstrate the specificity and sensitivity of this nanoparticle conjugate as a cancer imaging, therapy and sensing system in vitro.

Balalaeva, I. V., et al. (2012). "Passive and active targeting of quantum dots for whole-body fluorescence imaging of breast cancer xenografts." J Biophotonics **5**(11-12): 860-867.

Far-red and near-infrared fluorescent quantum dots (QDs) have become advancing contrast agents for efficient whole-body tumor imaging. In this study, we investigated the possibility of the vital fluorescence imaging of tumor using two contrast agents on the basis of QDs: bioinert QDs coated with polyethyleneglycol and QDs bound with anti-HER2/neu scFv antibodies. HER2/neu-positive breast cancer tumor xenografts in nude mice were used as a model. It was shown that both bioinert and tumor-targeted QD probes can be successfully applied for visualization of the tumor using in vivo imaging method, but fluorescent signal of QD-4D5scFv in tumors was considerably stronger than that of QD-PEG.

Bansal, S., et al. (2019). "Development of biosurfactant-based graphene quantum dot conjugate as a novel and fluorescent theranostic tool for cancer." Int J Nanomedicine **14**: 809-818.

BACKGROUND: Biosurfactants are amphipathic molecules of microbial origin that reduce surface and interfacial tension at gas-liquid-solid interfaces. Earlier, the biosurfactant was isolated and characterized in our laboratory from Candida parapsilosis. The property of the biosurfactant is further explored in this study by using quantum dots (QDs) as nanocarrier. MATERIALS AND METHODS: Graphene quantum dots (GQDs) were synthesized by bottom-up approach through pyrolysis of citric acid. GQDs were conjugated with both biosurfactant and folic acid (FA) using carbodiimide chemistry. The prepared GQD bioconjugate was studied for diagnostic and therapeutic effects against cancer cells. RESULTS AND DISCUSSION: Photoluminescence quantum yield (QY) of plain GQDs was measured as 12.8%. QY for biosurfactant conjugated GQDs and FA-biosurfactant conjugated GQDs was measured as 10.4% and 9.02%, respectively, and it was sufficient for targeting cancer cells. MTT assay showed that more than 90% of cells remained viable at concentration of 1 mg/mL, hence GQDs seemed to be non-toxic to cells. Biosurfactant conjugated GQDs caused 50% reduction in cellular viability within 24 hours. FA conjugation further increased the specificity of bioconjugated GQDs toward tumor cells, which is clearly evident from the drug internalization studies using confocal laser scanning microscopy. A higher amount of drug uptake was observed when bioconjugated GQDs were decorated with FA. CONCLUSION: The ability of GQD bioconjugate could be used as a theranostic tool for cancer. It is foreseen that in near future cancer can be detected and/or treated at an early stage by utilizing biosurfactant conjugated GQDs. Therefore, the proposed study would provide a stepping stone to improve the life of cancer patients.

Bao, Y. W., et al. (2018). "Hyperthemia-Promoted Cytosolic and Nuclear Delivery of Copper/Carbon Quantum Dot-Crosslinked Nanosheets: Multimodal Imaging-Guided Photothermal Cancer Therapy." ACS Appl Mater Interfaces **10**(2): 1544-1555.

Copper-containing nanomaterials have been applied in various fields because of their appealing physical, chemical, and biomedical properties/functions. Herein, for the first time, a facile, room-temperature, and one-pot method of simply mixing copper ions and sulfur-doped carbon dots (CDs) is developed for the synthesis of copper/carbon quantum dot (or CD)-crosslinked nanosheets (CuCD NSs). The thus-obtained CuCD NSs with the size of 20-30 nm had a high photothermal conversion efficiency of 41.3% and good photothermal stability. Especially, after coating with thiol-polyethylene glycol and fluorescent molecules, the resultant CuCD NSs could selectively target tumor tissues and realize multimodal (photoacoustic, photothermal, and fluorescence) imaging-guided cancer therapy. More importantly, our CuCD NSs exhibited laser-triggered cytosolic delivery, lysosomal escape, and nuclear-targeting properties, which greatly enhanced

their therapeutic efficacy. The significantly enhanced tumor accumulation of CuCD NSs after in situ tumor-site laser irradiation was also observed in in vivo experiments. These in vitro and in vivo events occurring during the continuous laser irradiation have not been observed. Overall, this work develops a CD-assisted synthetic method of photothermal nanoagents for triple-modal imaging-guided phototherapy and deepens our understanding of the action mechanism of photothermal therapy, which will promote the development of nanomedicine and beyond.

Barat, B., et al. (2009). "Cys-diabody quantum dot conjugates (immunoQdots) for cancer marker detection." Bioconjug Chem **20**(8): 1474-1481.

The present work demonstrates the use of small bivalent engineered antibody fragments, cys-diabodies, for biological modification of nanoscale particles such as quantum dots (Qdots) for detection of target antigens. Novel bioconjugated quantum dots known as immunoQdots (iQdots) were developed by thiol-specific oriented coupling of tumor specific cys-diabodies, at a position away from the antigen binding site to amino PEG CdSe/ZnS Qdots. Initially, amino PEG Qdot 655 were coupled with reduced anti-HER2 cys-diabody by amine-sulfhydryl-reactive linker [N-epsilon-maleimidocaproyloxy] succinimide ester (EMCS) to produce anti-HER2 iQdot 655. Spectral characterization of the conjugate revealed that the spectrum was symmetrical and essentially identical to unconjugated Qdot. Specific receptor binding activity of anti-HER2 iQdot 655 was confirmed by flow cytometry on HER2 positive and negative cells. Immunofluorescence results showed homogeneous surface labeling of the cell membrane with Qdot 655 conjugate. In addition, cys-diabodies specific for HER2, as well as prostate stem cell antigen (PSCA), were conjugated successfully with amino PEG Qdot 800. All of these iQdots retain the photoluminescence properties of the unconjugated Qdot 800 as well as the antigen binding specificity of the cys-diabody as demonstrated by flow cytometry. Simultaneous detection of two tumor antigens on LNCaP/PSCA prostate cancer cells (which express PSCA and HER2) in culture was possible using two iQdots, anti-HER2 iQdot 655 and anti-PSCA iQdot 800. Thus, these iQdots are potentially useful as optical probes for sensitive, multiplexed detection of surface markers on tumor cells. The present thiol-specific conjugation method demonstrates a general approach for site-specific oriented coupling of cys-diabodies to a wide variety of nanoparticles without disturbing the antigen binding site and maintaining small size compared to intact antibody.

Barati, F., et al. (2020). "Highly efficient detection of cancer-derived exosomes using modified core-shell electrospun nanofibers as a capture substrate and antibody immobilized-graphene quantum dots as a signaling agent." Anal Methods **12**(28): 3670-3681.

In the past few years graphene quantum dots (GQDs) have been used as a signaling agent for medical diagnosis. They can be modified and labeled with different macromolecules to give them potential to be attached to a specific target. Herein GQDs were labeled with an antibody which is specific for cancer-derived exosomes, isolated from blood serum by using a specialized PCL-gelatin core-shell NFM. This membrane showed excellent sensitivity for isolating exosomes from a complex mixture such as serum, and the GQD-antibody complex detected the isolated exosomes with great sensitivity. The final results allow this method to be considered as one that can be used to quantify the concentration of a desired analyte in a mixture.

Barua, S. and K. Rege (2009). "Cancer-cell-phenotype-dependent differential intracellular trafficking of unconjugated quantum dots." Small **5**(3): 370-376.

A diverse array of nanoparticles, including quantum dots (QDs), metals, polymers, liposomes, and dendrimers, are being investigated as therapeutics and imaging agents in cancer diseases. However, the role of the cancer-cell phenotype on the uptake and intracellular fate of nanoparticles in cancer cells remains poorly understood. Reported here is that differences in cancer-cell phenotypes can lead to significant differences in intracellular sorting, trafficking, and localization of nanoparticles. Unconjugated anionic QDs demonstrate dramatically different intracellular profiles in three closely related human-prostate-cancer cells used in the investigation: PC3, PC3-flu, and PC3-PSMA. QDs demonstrate punctated intracellular localization throughout the cytoplasm in PC3 cells. In contrast, the nanoparticles localize mainly at a single juxtanuclear location ("dot-of-dots") inside the perinuclear recycling compartment in PC3-PSMA cells, where they co-localize with transferrin and the prostate-specific membrane antigen. The results indicate that nanoparticle sorting and transport is influenced by changes in cancer-cell phenotype and can have significant implications in the design and engineering of nanoscale drug delivery and imaging systems for advanced tumors.

Bentolila, L. A., et al. (2005). "Quantum dots for molecular imaging and cancer medicine." Discov Med **5**(26): 213-218.

Extract: The past few decades have witnessed technical advances that have introduced cell biologists and physicians to a new, dynamic, subcellular world where genes and gene products can be visualized to interact in space and time and in health and disease. The accelerating field of molecular imaging has been

critically dependent on indicator probes which show when and where genetically or biochemically defined molecules, signals or processes appear, interact and disappear, with high spatial and temporal resolution in living cells and whole organisms. For example, the use of radionuclide tracers combined with 3-dimensional (3-D) imaging systems such as Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are now helping clinicians to characterize the molecular status of tumors deep within patients. Other types of imaging probes rely on the bioluminescence and fluorescence of genetically encoded proteins (originally found in fireflies and jellyfish, respectively) or entirely synthetic fluorochromes, or a combination of both. New powerful biological fluorescence microscopes provide the ability to study single molecules within single cells. Multiphoton confocal microscopy has been developed to allow for the capturing of high-resolution, 3-D images of living tissues that have been tagged with highly specific fluorophores.

Bharathi, G., et al. (2021). "An all-graphene quantum dot Forster resonance energy transfer (FRET) probe for ratiometric detection of HE4 ovarian cancer biomarker." Colloids Surf B Biointerfaces **198**: 111458.

Ovarian cancer (OVC), the most lethal form of all gynecological cancers, is a big threat to women's health. Late diagnosis at the advanced stages is one of the major reasons for the ovarian cancer-related deaths. Conventionally, the up-regulated proteins CA125 (cancer antigen 125) and HE4 (human epididymis protein 4) are used as biomarkers to diagnose the OVC malignancies. The lack of sensitivity/specificity and the false-positive results create complexity in the diagnostic process. With specificity over 90 %, HE4 is suitable for diagnosing ovarian cancer. Herein, we have developed an ultrasensitive all-graphene quantum dot (GQD) Forster resonance energy transfer (FRET) probe for the ratiometric detection of HE4 biomarker. A set of two GQD samples were solvothermally prepared and then analyzed by the morphological, structural, and photophysical characterization. One GQD sample exhibited a strong green emission, peaked at around 515 nm, while the other GQD sample displayed a strong red emission with maximum at around 615 nm. The good spectral overlap between the emission and excitation spectra of the green and red GQDs, respectively, all allowed us to consider them for the design of FRET-based probe. The green and red-emitting GQDs were conjugated with HE4 antibody and used as donor and acceptor, respectively for the ratiometric sensing of HE4 ovarian cancer biomarker. The all GQD FRET probe was able to detect as low as 4.8 pM, along with a large dynamic detection range up to 300 nM. The selectivity and interference effect of the developed FRET probe was also investigated against different protein combinations.

Bhowal, S., et al. (2018). "A novel metallogel based approach to synthesize (Mn, Cu) doped ZnS quantum dots and labeling of MCF-7 cancer cells." Dalton Trans **47**(18): 6557-6569.

The present study aims to formulate a common synthetic strategy for preparing quantum dots (QDs) in a greener way by using combination of popular methods, viz. a colloidal method with suitable capping agent and low molecular weight gel based synthesis. Pyridine dicarboxylic acid (PDC) in presence of AlCl3 forms a stable metallogel, which serves as an excellent medium for selective ZnS QD synthesis. The aromatic pyridine moiety, well known for being a capping agent, indeed plays its part in the run up to QD synthesis. To the best of our knowledge, this is the first example of a metallogel based doped ZnS QD synthesis. Altering the doping material and its composition changes the properties of the QDs, but herein we also tried to establish how these changes affect the gel morphology and stability of both gel and QDs. We further demonstrate, by using live cell confocal microscopy, the delivery of QDs Cu ZnS and MnZnS nanomaterials in the nucleus and the cytoplasm of human breast cancer cells (MCF7), implicating the use of metallogel based QDs for bio-imaging and bio-labeling.

Biagiotti, G., et al. (2021). "Glyco-Coated CdSe/ZnS Quantum Dots as Nanoprobes for Carbonic Anhydrase IX Imaging in Cancer Cells." ACS Appl Nano Mater **4**(12): 14153-14160.

The bioimaging of cancer cells by the specific targeting of overexpressed biomarkers is an approach that holds great promise in the identification of selective diagnostic tools. Tumor-associated human carbonic anhydrase (hCA) isoforms IX and XII have been considered so far as well-defined biomarkers, with their expression correlating with cancer progression and aggressiveness. Therefore, the availability of highly performant fluorescent tools tailored for their targeting and able to efficiently visualize such key targets is in high demand. We report here on the design and synthesis of a kind of quantum dot (QD)-based fluorescent glyconanoprobe coated with a binary mixture of ligands, which, according to the structure of the terminal domains, impart specific property sets to the fluorescent probe. Specifically, monosaccharide residues ensured the dispersibility in the biological medium, CA inhibitor residues provided specific targeting of membrane-anchored hCA IX overexpressed on bladder cancer cells, and the quantum dots imparted the optical/fluorescence properties.

Biava, P. M., et al. (2019). "Stem Cell Differentiation Stage Factors and their Role in Triggering Symmetry Breaking Processes during Cancer Development: A Quantum Field Theory Model for Reprogramming Cancer Cells to Healthy Phenotypes." Curr Med Chem **26**(6): 988-1001.

A long history of research has pursued the use of embryonic factors isolated during cell differentiation processes for the express purpose of transforming cancer cells back to healthy phenotypes. Recent results have clarified that the substances present at different stages of cell differentiation-which we call stem cell differentiation stage factors (SCDSFs)-are proteins with low molecular weight and nucleic acids that regulate genomic expression. The present review summarizes how these substances, taken at different stages of cellular maturation, are able to retard proliferation of many human tumor cell lines and thereby reprogram cancer cells to healthy phenotypes. The model presented here is a quantum field theory (QFT) model in which SCDSFs are able to trigger symmetry breaking processes during cancer development. These symmetry breaking processes, which lie at the root of many phenomena in elementary particle physics and condensed matter physics, govern the phase transitions of totipotent cells to higher degrees of diversity and order, resulting in cell differentiation. In cancers, which share many genomic and metabolic similarities with embryonic stem cells, stimulated redifferentiation often signifies the phenotypic reversion back to health and nonproliferation. In addition to acting on key components of the cellular cycle, SCDSFs are able to reprogram cancer cells by delicately influencing the cancer microenvironment, modulating the electrochemistry and thus the collective electrodynamic behaviors between dipole networks in biomacromolecules and the interstitial water field. Coherent effects in biological water, which are derived from a dissipative QFT framework, may offer new diagnostic and therapeutic targets at a systemic level, before tumor instantiation occurs in specific tissues or organs. Thus, by including the environment as an essential component of our model, we may push the prevailing paradigm of mutation-driven oncogenesis toward a closer description of reality.

Biju, V., et al. (2010). "Bioconjugated quantum dots for cancer research: present status, prospects and remaining issues." Biotechnol Adv **28**(2): 199-213.

Semiconductor quantum dots (QDs) are nanoparticles in which charge carriers are three dimensionally confined or quantum confined. The quantum confinement provides size-tunable absorption bands and emission color to QDs. Also, the photoluminescence (PL) of QDs is exceptionally bright and stable, making them potential candidates for biomedical imaging and therapeutic interventions. Although fluorescence imaging and photodynamic therapy (PDT) of cancer have many advantages over imaging using ionizing radiations and chemo and radiation therapies, advancement of PDT is limited due to the poor availability of photostable and NIR fluorophores and photosensitizing (PS) drugs. With the introduction of biocompatible and NIR QDs, fluorescence imaging and PDT of cancer have received new dimensions and drive. In this review, we summarize the prospects of QDs for imaging and PDT of cancer. Specifically, synthesis of visible and NIR QDs, targeting cancer cells with QDs, in vitro and in vivo cancer imaging, multimodality, preparation of QD-PS conjugates and their energy transfer, photosensitized production of reactive oxygen intermediates (ROI), and the prospects and remaining issues in the advancement of QD probes for imaging and PDT of cancer are summarized.

Bilan, R., et al. (2017). "Quantum-dot-based suspension microarray for multiplex detection of lung cancer markers: preclinical validation and comparison with the Luminex xMAP((R)) system." Sci Rep **7**: 44668.

A novel suspension multiplex immunoassay for the simultaneous specific detection of lung cancer markers in bronchoalveolar lavage fluid (BALF) clinical samples based on fluorescent microspheres having different size and spectrally encoded with quantum dots (QDEM) was developed. The designed suspension immunoassay was validated for the quantitative detection of three lung cancer markers in BALF samples from 42 lung cancer patients and 10 control subjects. Tumor markers were detected through simultaneous formation of specific immune complexes consisting of a capture molecule, the target antigen, and biotinylated recognition molecule on the surface of the different QDEM in a mixture. The immune complexes were visualized by fluorescently labeled streptavidin and simultaneously analyzed using a flow cytometer. Preclinical validation of the immunoassay was performed and results were compared with those obtained using an alternative 3-plex immunoassay based on Luminex xMAP((R)) technology, developed on classical organic fluorophores. The comparison showed that the QDEM and xMAP((R)) assays yielded almost identical results, with clear discrimination between control and clinical samples. Thus, developed QDEM technology can become a good alternative to xMAP((R)) assays permitting analysis of multiple protein biomarkers using conventional flow cytometers.

Birma Bwatanglang, I., et al. (2017). "Histological analysis of anti-cancer drug loaded, targeted Mn:ZnS quantum dots in metastatic lesions of 4T1 challenged mice." J Mater Sci Mater Med **28**(9): 138.

5-Fluororaucil (5-FU) as anti-cancer drug was reported to induce thymidine synthase (TS) overexpression and cancer cell resistance. To improve its therapeutic efficacy and selective targeting, here we developed a targeted delivery system mediated by the active ligand-folate receptor chemistry to deliver the 5-FU drug selectively into the tumor microenvironment. The preparation was achieved by exploring chitosan (CS)-biopolymer based system with folic acid (FA)-conjugation. The 5-FU@FACS-Mn:ZnS quantum dots (QDs) based on the histological assessment conducted in the 4T1 challenged mice showed an improved tumor remission in the liver, spleen and lungs. The 5-FU@FACS-Mn:ZnS composite induced anti-proliferative properties in these organs as compared to the free 5-FU drug. Unlike the 5-FU@FACS-Mn:ZnS treated groups which showed some specific morphological changes such as cell shrinkage without obvious presence of adipocytes, the excised section of the tumor in the untreated control group and the free 5-FU drug treated group showed necrotic and degenerated cells; these cells are multifocally distributed in the tumor mass with evidence of widely distributed adipocytes within the tumor mass. These findings suggest that the 5-FU@FACS-Mn:ZnS composite has a superior role during the induction of apoptosis in the 4T1 cells as compared to the free 5-FU drug treated groups. The results of the study therefore suggest that the impregnation of 5-FU anti-cancer drug within the FACS-Mn:ZnS system significantly improves its selective targeting efficacy, in addition to improving the anti-proliferative properties and attenuate possible tumor resistances to the 5-FU drug. The work discusses about the anti-metastatic effects of folic acid-bound 5-Fluororacil loaded Mn:ZnS quantum dots towards 4T1 cell line proliferation in mice based on the histological analysis.

Bostick, R. M., et al. (2006). "Detecting and quantifying biomarkers of risk for colorectal cancer using quantum dots and novel image analysis algorithms." Conf Proc IEEE Eng Med Biol Soc **2006**: 3313-3316.

Colorectal cancer, the second leading cause of cancer deaths in the United States, is a molecular disease that is largely lifestyle determined and preventable. While heart disease has been sharply declining, in large part from widespread use of biological measurements that indicate risk ("biomarkers of risk"), such as blood cholesterol, to motivate and guide preventive treatment, colorectal cancer is a disease for which mortality rates have changed little and for which there have been no biomarkers of risk. Based on new knowledge about the molecular basis of colorectal cancer we developed and validated a panel of treatable biomarkers of risk that can be measured in rectal biopsies using automated immunohistochemistry and semi-automated image analysis. The methodology is now being made practical for clinical application through the use of 1) quantum dots, so that all of the biomarkers can be detected simultaneously on the same histologic sections (i.e., multiplexed), and 2) novel, automated image analysis algorithms to measure the quantities and tissue distributions of the biomarkers. Herein we summarize our methods, results, current directions, and progress.

Brakmane, G., et al. (2013). "Cancer antibody enhanced real time imaging cell probes--a novel theranostic tool using polymer linked carbon nanotubes and quantum dots." Anticancer Agents Med Chem **13**(5): 821-832.

BACKGROUND: Cancer is a potentially fatal diagnosis, but due to modern medicine there is a potential cure in many of these cases. The rate of treatment success depends on early disease detection and timely, effective delivery of tumour specific treatment. There are many ongoing researches aimed to improve diagnostics or treatment, but the option to use both modalities concomitantly is deficient. In this project we are using the advances in nanotechnology to develop new theranostic tool using single walled carbon nanotubes (SWCNT) and Quantum dots (QDs) for early cancer cell detection, and option to deliver targeted treatment. METHOD: SWCNTs were refluxed in HNO3/H2SO4 (1:3) at 120 masculineC for 120 minutes. Functionalised SWCNT was then covalently attached to octa-ammonium polyhedral oligomeric silsesquioxane (POSS), QDs and conjugated with antibodies for targeted cell detection. Fourier transforms infrared spectroscopy (FTIR), Transmission electron microscopy (TEM), UV/NIR analysis, Raman and UV-VIS spectroscopy were used in order to prove the successful conjugation. Toxicology study using alamar blue analysis and DNA assay was conducted in order to choose the best concentration of SWCNT, octa-ammonium-POSS and QDs before commencing the conjugation process. Human colorectal cancer cell line HT29, pancreas cancer cell line PANC-1 and mouse fibroblasts 3T3 were then treated with or without antibody conjugated SWCNT-POSS-QDs (CPQ) compound solution. The cell response was observed under the microscope after 24, 48 and 72 hours. RESULTS: FTIR and Raman spectroscopies confirmed covalent binding of the SWCNTs to Octa-Ammonium-POSS. This was supported by TEM images and photos obtained, which showed well dispersed SWCNTs following its treatment with Octa-Ammonium-POSS compared to pristine SWCNT samples. UV-VIS graphs determined the presence of antibody within the compound. UV/NIR demonstrated QD fluorescence even after attachment of SWCNT-POSS. The cellular behaviour revealed high CPQ-antibody complex affinity towards cancer cells when compared to healthy cell line which internalised the complex only on day three. The

pancreas cancer cell line had appearance of lysed pulp after 72 hours of incubation. Colonic cancer cells seemed to regain ability to populate from day three signifying that higher treatment payload is necessary. CONCLUSION: We have successfully manufactured novel compound consisting of Octa-Ammonium-POSS linked SWCNTs, QDs, and tumour specific antibodies. The complex has proven its potential as cell probing tool, and the attachment of antibodies has shown high affinity to cancer cells rendering this an attractive model for further theranostic developments.

Bwatanglang, I. B., et al. (2016). "Folic acid targeted Mn:ZnS quantum dots for theranostic applications of cancer cell imaging and therapy." Int J Nanomedicine **11**: 413-428.

In this study, we synthesized a multifunctional nanoparticulate system with specific targeting, imaging, and drug delivering functionalities by following a three-step protocol that operates at room temperature and solely in aqueous media. The synthesis involves the encapsulation of luminescent Mn:ZnS quantum dots (QDs) with chitosan not only as a stabilizer in biological environment, but also to further provide active binding sites for the conjugation of other biomolecules. Folic acid was incorporated as targeting agent for the specific targeting of the nanocarrier toward the cells overexpressing folate receptors. Thus, the formed composite emits orange-red fluorescence around 600 nm and investigated to the highest intensity at Mn(2+) doping concentration of 15 at.% and relatively more stable at low acidic and low alkaline pH levels. The structural characteristics and optical properties were thoroughly analyzed by using Fourier transform infrared, X-ray diffraction, dynamic light scattering, ultraviolet-visible, and fluorescence spectroscopy. Further characterization was conducted using thermogravimetric analysis, high-resolution transmission electron microscopy, field emission scanning electron microscopy, energy dispersive X-ray spectroscopy, X-ray fluorescence, and X-ray photoelectron spectroscopy. The cell viability and proliferation studies by means of MTT assay have demonstrated that the as-synthesized composites do not exhibit any toxicity toward the human breast cell line MCF-10 (noncancer) and the breast cancer cell lines (MCF-7 and MDA-MB-231) up to a 500 microg/mL concentration. The cellular uptake of the nanocomposites was assayed by confocal laser scanning microscope by taking advantage of the conjugated Mn:ZnS QDs as fluorescence makers. The result showed that the functionalization of the chitosan-encapsulated QDs with folic acid enhanced the internalization and binding affinity of the nanocarrier toward folate receptor-overexpressed cells. Therefore, we hypothesized that due to the nontoxic nature of the composite, the as-synthesized nanoparticulate system can be used as a promising candidate for theranostic applications, especially for a simultaneous targeted drug delivery and cellular imaging.

Cai, X., et al. (2016). "pH-Sensitive ZnO Quantum Dots-Doxorubicin Nanoparticles for Lung Cancer Targeted Drug Delivery." ACS Appl Mater Interfaces **8**(34): 22442-22450.

In this paper, we reported a ZnO quantum dots-based pH-responsive drug delivery platform for intracellular controlled release of drugs. Acid-decomposable, luminescent aminated ZnO quantum dots (QDs) were synthesized as nanocarriers with ultrasmall size (approximately 3 nm). The dicarboxyl-terminated poly(ethylene glycol) (PEG) had been introduced to NH2-ZnO QDs, which rendered it stable under physiological fluid. Moreover, a targeting ligand, hyaluronic acid (HA), was conjugated to ZnO QDs for specifically binding to the overexpressed glycoprotein CD44 by cancer cells. Doxorubicin (DOX) molecules were successfully loaded to PEG functionalized ZnO QDs via formation of metal-DOX complex and covalent interactions. The pH-sensitive ZnO QDs dissolved to Zn(2+) in acidic endosome/lysosome after uptake by cancer cells, which triggered dissociation of the metal-drug complex and a controlled DOX release. As result, a synergistic therapy was achieved due to incorporation of the antitumor effect of Zn(2+) and DOX.

Camargo, L. T., et al. (2009). "A quantum chemical and chemometrical study of indolo[2,1-b]quinazoline and their analogues with cytotoxic activity against breast cancer cells." SAR QSAR Environ Res **20**(5-6): 537-549.

Some indolo[2,1-b]quinalozine (tryptanthrin) analogues present cytotoxic activity against human breast cancer cells. In this work, chemometric methods were applied in the search for building discriminant models between active and inactive analogues, based on the correlations among their in vitro cytotoxic activities and their electronic and geometric molecular descriptors. From 88 descriptors calculated with density functional theory with the exchange correlation functional B3LYP and the basis set 6-31G* (Gaussian 03), 29 were pre-selected based on their Fisher weights, and finally five descriptors (partial charge on atom 15, bond orders between atoms 12-13, 17-25 and 18-26, and energy difference between frontier molecular orbitals) were selected for principal component analysis. This analysis was able to discriminate 12 inactive from 22 active analogues by using only one principal component, accounting for 49% of the total variance and allowing us to better understand the influence of these electronic descriptors in the cytotoxic activity. In addition, a supervised partial least-squares discriminant model was

build and successfully used to discriminate tryptanthrin analogues. The model was validated through an independent test set and considered robust to overfitting.

Campbell, E., et al. (2019). "Doped Graphene Quantum Dots for Intracellular Multicolor Imaging and Cancer Detection." ACS Biomater Sci Eng **5**(9): 4671-4682.

Despite significant advances of nanomedicine, the issues of biocompatibility, accumulation-derived toxicity, and the lack of sensing and in vivo imaging capabilities hamper the translation of most nanocarriers into clinic. To address this, we utilize nitrogen, boron/nitrogen, and sulfur-doped graphene quantum dots (GQDs) as fully biocompatible multifunctional platforms allowing for multicolor visible/near-IR imaging and cancer-sensing. These GQDs are scalably produced in one-step synthesis from a single biocompatible glucosamine precursor, are water-soluble, show no cytotoxicity at high concentrations of 1 mg/mL, and demonstrate substantial degradation at 36 h in biological environments as verified by TEM imaging. Because of their small sizes, GQDs exhibit efficient internalization maximized at 12 h followed by further degradation/excretion. Their high-yield intrinsic fluorescence in blue/green and near-infrared allows for multicolor in vitro imaging on its own or in combination with other fluorophores, and offers the capabilities for in vivo near-IR fluorescence tracking. Additionally, nitrogen- and sulfur-doped GQDs exhibit pH-dependent fluorescence response that is successfully utilized as a sensing mechanism for acidic extracellular environments of cancer cells. It allows for the deterministic, ratiometric spectral discrimination between cancerous (HeLa and MCF-7 cell) versus healthy (HEK-293 cell) environments with substantial intensity ratios of 1.6 to 8. These results suggest fully biocompatible GQDs developed in this work as multifunctional candidates for in vitro delivery of active agents, multicolor visible/near-IR fluorescence imaging, and pH-sensing of cancerous environments.

Campbell, E., et al. (2021). "Graphene quantum dot formulation for cancer imaging and redox-based drug delivery." Nanomedicine **37**: 102408.

This work develops a new multifunctional biocompatible anticancer nanoformulation to provide targeted image-guided cancer-selective therapeutics. It consists of three active covalently bound components: (1) biocompatible nitrogen-doped graphene quantum dots (GQDs) as a multifunctional delivery and imaging platform, (2) hyaluronic acid (HA) unit targeted to the CD44 receptors on a variety of cancer cells, and (3) oxidative stress-based cancer-selective ferrocene (Fc) therapeutic. The biocompatible GQD platform synthesized from glucosamine exhibits high-yield intrinsic fluorescence. It is utilized for tracking Fc-GQD-HA formulation in vitro indicating internalization enhancement in HeLa cells targeted by the HA over non-cancer HEK-293 cells not overexpressing CD44 receptor. Fc-GQD-HA, non-toxic at 1 mg/mL to HEK-293 cells, induces cytotoxic response in HeLa enhanced over time, while therapeutic ROS generation by Fc-GQD-HA is ~3 times greater than that of Fc alone. This outlines the targeted delivery, imaging, and cancer-specific treatment capabilities of the new Fc-GQD-HA formulation enabling desired cancer-focused nanotherapeutic approach.

Cao, J. T., et al. (2015). "Versatile Microfluidic Platform for the Assessment of Sialic Acid Expression on Cancer Cells Using Quantum Dots with Phenylboronic Acid Tags." ACS Appl Mater Interfaces **7**(27): 14878-14884.

This work describes a versatile microfluidic platform for evaluation of cell-surface glycan expression at the single-cell level using quantum dots (QDs) tagged with phenylboronic acid. The platform was integrated with dual microwell arrays, allowing the introduction of cells in two states using the same cell culture chamber. The simultaneous analysis of cells in the same environment minimized errors resulting from different culture conditions. As proof-of-concept, the expressions of sialic acid (SA) groups on K562 cells, with or without 3'-azido-3'-deoxythymidine (AZT) treatment, were evaluated in the same chamber. 3-Aminophenylboronic acid functionalized CdSeTe@ZnS-SiO2 QDs (APBA-QDs) were prepared as probes to recognize SA groups on K562 cells with only one-step labeling. The results showed that the expression of SA moieties on K562 cells was increased by 18% and 31% after treatment with 20 and 40 muM AZT, respectively. Performing the drug treatment and control experiments simultaneously in the same chamber significantly improved the robustness and effectiveness of the assay. The strategy presented here provides an alternative tool for glycan analysis in a sensitive, high-throughput, and effective manner.

Cao, Y., et al. (2022). "Dual-color quantum dot-loaded nanoparticles based lateral flow biosensor for the simultaneous detection of gastric cancer markers in a single test line." Anal Chim Acta **1218**: 339998.

A dual-color quantum dots-loaded nanoparticles (QPs) based lateral flow biosensor with single test line has been developed. Red and green emitted QPs were conjugated with antibodies and served as detecting probes in assays respectively, while the mixture of various antibodies were immobilized on nitrocellulose membranes as one detection line. Benefit from eliminating the heterogeneity caused by different position on the membrane, current biosensor achieved higher accuracy comparing with prevalent multi-lines or multi-strips lateral flow systems, which is of great

significance for analyzing ratio-related diagnostics. The capability and reliability of the multiplex biosensor are also demonstrated by utilizing pepsinogen I (PG I) and pepsinogen II (PG II) as the model analytes. Under the optimal conditions, quantitative detection was achieved with ultra-low limits of detection at 6.9 pM (0.29 ng mL(-1), PG I) and 15.7 pM (0.66 ng mL(-1), PG II) respectively. The spectra crosstalk was negligible and no apparent cross-reaction was found in simultaneous detection. Furthermore, a good linear correlation of the QPs based lateral flow biosensor and commercial time-resolved fluoroimmunoassay was obtained in the detection of clinical samples, indicating the high reliability of the proposed biosensor.

Cao, Y., et al. (2017). "Aptamer-Conjugated Graphene Quantum Dots/Porphyrin Derivative Theranostic Agent for Intracellular Cancer-Related MicroRNA Detection and Fluorescence-Guided Photothermal/Photodynamic Synergetic Therapy." ACS Appl Mater Interfaces **9**(1): 159-166.

Multifunctional theranostic platform coupling diagnostic and therapeutic functions holds great promise for personalized nanomedicine. Nevertheless, integrating consistently high performance in one single agent is still challenging. This work synthesized a sort of porphyrin derivatives (P) with high singlet oxygen generation ability and graphene quantum dots (GQDs) possessing good fluorescence properties. The P was conjugated to polyethylene glycol (PEG)ylated and aptamer-functionalized GQDs to gain a multifunctional theranostic agent (GQD-PEG-P). The resulting GQD-PEG-P displayed good physiological stability, excellent biocompatibility and low cytotoxicity. The intrinsic fluorescence of the GQDs could be used to discriminate cancer cells from somatic cells, whereas the large surface facilitated gene delivery for intracellular cancer-related microRNA (miRNA) detection. Importantly, it displayed a photothermal conversion efficiency of 28.58% and a high quantum yield of singlet oxygen generation up to 1.08, which enabled it to accomplish advanced photothermal therapy (PTT) and efficient photodynamic therapy (PDT) for cancer treatment. The combined PTT/PDT synergic therapy led to an outstanding therapeutic efficiency for cancer cell treatment.

Carbary-Ganz, J. L., et al. (2014). "Quantum dots targeted to vascular endothelial growth factor receptor 2 as a contrast agent for the detection of colorectal cancer." J Biomed Opt **19**(8): 086003.

We successfully labeled colorectal cancer in vivo using quantum dots targeted to vascular endothelial growth factor receptor 2 (VEGFR2). Quantum dots with emission centered at 655 nm were bioconjugated to anti-VEGFR2 antibodies through streptavidin/biotin linking. The resulting QD655-VEGFR2 contrast agent was applied in vivo to the colon of azoxymethane (AOM) treated mice via lavage and allowed to incubate. The colons were then excised, cut longitudinally, opened to expose the lumen, and imaged en face using a fluorescence stereoscope. The QD655-VEGFR2 contrast agent produced a significant increase in contrast between diseased and undiseased tissues, allowing for fluorescence-based visualization of the diseased areas of the colon. Specificity was assessed by observing insignificant contrast increase when labeling colons of AOM-treated mice with quantum dots bioconjugated to isotype control antibodies, and by labeling the colons of saline-treated control mice. This contrast agent has a great potential for in vivo imaging of the colon through endoscopy.

Carbary-Ganz, J. L., et al. (2015). "In vivo molecular imaging of colorectal cancer using quantum dots targeted to vascular endothelial growth factor receptor 2 and optical coherence tomography/laser-induced fluorescence dual-modality imaging." J Biomed Opt **20**(9): 096015.

Optical coherence tomography/laser induced fluorescence (OCT/LIF) dual-modality imaging allows for minimally invasive, nondestructive endoscopic visualization of colorectal cancer in mice. This technology enables simultaneous longitudinal tracking of morphological (OCT) and biochemical (fluorescence) changes as colorectal cancer develops, compared to current methods of colorectal cancer screening in humans that rely on morphological changes alone. We have shown that QDot655 targeted to vascular endothelial growth factor receptor 2 (QD655-VEGFR2) can be applied to the colon of carcinogen-treated mice and provides significantly increased contrast between the diseased and undiseased tissue with high sensitivity and specificity ex vivo. QD655-VEGFR2 was used in a longitudinal in vivo study to investigate the ability to correlate fluorescence signal to tumor development. QD655-VEGFR2 was applied to the colon of azoxymethane (AOM-) or saline-treated control mice in vivo via lavage. OCT/LIF images of the distal colon were taken at five consecutive time points every three weeks after the final AOM injection. Difficulties in fully flushing unbound contrast agent from the colon led to variable background signal; however, a spatial correlation was found between tumors identified in OCT images, and high fluorescence intensity of the QD655 signal, demonstrating the ability to detect VEGFR2 expressing tumors in vivo.

Carvalho, I. C., et al. (2019). "L-cysteine and poly-L-arginine grafted carboxymethyl cellulose/Ag-In-S quantum dot fluorescent nanohybrids for in vitro

bioimaging of brain cancer cells." Int J Biol Macromol **133**: 739-753.

Although noticeable scientific and technological progress, cancer remains one of the deadliest diseases worldwide and advancements in diagnosis, targeting and treating cancer cells are an urgency. In this study, we designed and synthesized novel amino acid and polypeptide modified polysaccharide derivatives associated with fluorescent nanomaterials for producing nanohybrids with functionalities for bioimaging and cell penetrating. Carboxymethylcellulose (CMCel) was chemically biofunctionalized with L-cysteine (CMCelCys) or poly-L-arginine (CMCelPolyArg) and the conjugates were used as capping ligands for synthesizing fluorescent AgInS2 quantum dots (AIS-QDs) in aqueous colloidal media. These systems were characterized by FTIR, NMR, UV-Vis, TEM-EDX, DLS, zeta potential and PL for assessing physicochemical properties, structural and morphological features. Mitochondrial activity assay (MTT) was used for evaluating preliminary cytotoxicity and confocal laser microscopy for investigating cellular uptake of the nanohybrids. Results confirmed the biofunctionalization of CMCel through amide bonds formation and indicated the formation of water-dispersed fluorescent nanocolloids with core-shell nanostructures composed by semiconductor cores stabilized by shell layers of CMCelCys or CMCelPolyArg. The nanohybrids' optical properties were affected by the grafting of functionalities into CMCel. All nanohybrids demonstrated no in vitro cytotoxicity based on MTT results and were successfully internalized by glioma cells, behaving as fluorescent nanoprobes for bioimaging and biolabeling.

Carvalho, M. E. T., et al. (2019). "Evaluating the glycophenotype on breast cancer tissues with quantum dots-Cramoll lectin conjugates." Int J Biol Macromol **138**: 302-308.

During carcinogenesis, changes in the glycosylation can modulate many biological processes. Thus, the interest in exploring and understanding the roles of carbohydrates as cancer biomarkers has been increasing. Lectins have been applied as useful tools in glycobiology, especially when associated with fluorescent reporters. Therefore, to take advantage of the physicochemical properties of quantum dots (QDs), herein, we conjugated Cramoll, a lectin that recognizes glucose/mannose residues, with those nanoparticles. We applied the conjugates to investigate the glycocode of normal, fibroadenoma (FB), and invasive ductal carcinoma (IDC) human breast tissues. Additionally, we proposed a method to quantitatively evaluate the tissue labeling intensity by a fluorescence microplate assay (FMA). Conjugates showed intense fluorescence and specificity. The lectin activity and secondary structure were also preserved after the conjugation with QDs. Moreover, fluorescence images showed that ductal cells of normal and FB tissues were preferentially labeled by conjugates, whereas both cells and stroma were strongly labeled in IDC. FMA showed in a quantitative, practical, and sensitive way that the level of exposed glucose/mannose residues increased accordingly to the sample malignancy degree. In conclusion, QDs-Cramoll conjugates can be considered effective, specific, and versatile probes to evaluate glycan profiles in normal and transformed tissues, by fluorescence microscopy as well as FMA quantification. Furthermore, FMA showed to be a potential method that can be applied with other fluorescent conjugates.

Chakraborty, P., et al. (2022). "Quantum dots: The cutting-edge nanotheranostics in brain cancer management." J Control Release **350**: 698-715.

Quantum dots (QDs) are semiconductor nanocrystals possessing unique optoelectrical properties in that they can emit light energy of specific tunable wavelengths when excited by photons. They are gaining attention nowadays owing to their all-around ability to allow high-quality bio-imaging along with targeted drug delivery. The most lethal central nervous system (CNS) disorders are brain cancers or malignant brain tumors. CNS is guarded by the blood-brain barrier which poses a selective blockade toward drug delivery into the brain. QDs have displayed strong potential to deliver therapeutic agents into the brain successfully. Their bio-imaging capability due to photoluminescence and specific targeting ability through the attachment of ligand biomolecules make them preferable clinical tools for coming times. Biocompatible QDs are emerging as nanotheranostic tools to identify/diagnose and selectively kill cancer cells. The current review focuses on QDs and associated nanoformulations as potential futuristic clinical aids in the continuous battle against brain cancer.

Chan, M. H., et al. (2019). "Development of upconversion nanoparticle-conjugated indium phosphide quantum dot for matrix metalloproteinase-2 cancer transformation sensing." Nanomedicine (Lond) **14**(14): 1791-1804.

Aim: Matrix metalloproteinase-2 (MMP2) plays an important role in extracellular matrix remodeling, that is, it increases significantly during cancer progression. In this regard, MMP2 monitoring is important. Experiment: A well-designed MMP2-sensitive polypeptide chain was used to link indium phosphide quantum dots (InP QDs) with upconversion nanoparticles (UCNPs) to form a nanocomposite that was utilized as biosensor. Results: We produced a biosensor that can be recognized by MMP2 and determined the presence or absence of MMP2 in cells by

identifying difference in fluorescence wavelength. The InP QDs modified the arginylglycylaspartic acid molecules as targeting ligand based on chitosan. Conclusion: The MMP2-based biosensor, named UCNP-p@InP-cRGD, is sensitive and can be applied for biosensing probes.

Chang, B., et al. (2013). "Water soluble fluorescence quantum dot probe labeling liver cancer cells." J Mater Sci Mater Med **24**(11): 2505-2508.

Water soluble quantum dots (QDs) have been prepared by hydrothermal method and characterized by ultraviolet irradiation, XRD, TEM, UV-Vis absorption spectrometer and fluorescence spectrometer. Then the QD-antibody-AFP probes (QD-Ab-AFP) were synthesized by chemical process and specifically labeled AFP antigen in PLC/PRF/5 liver cancer cells. The results showed that the QDs were cubic structure and had excellent optical properties. Moreover, the QD-Ab-AFP with good stability could specifically label liver cancer cells. This work provides strong foundation for further studying and developing new approach to detect liver cancer at early stage.

Chatterjee, S., et al. (2013). "An e-nose made of carbon nanotube based quantum resistive sensors for the detection of eighteen polar/nonpolar VOC biomarkers of lung cancer." J Mater Chem B **1**(36): 4563-4575.

A room temperature operating electronic nose (e-nose) has been developed by the assembly of conductive polymer nanocomposite (CPC) quantum resistive sensors (QRS). The fabrication of QRS by spray layer by layer (sLbL) of CPC solutions allowed us to obtain transducers with reproducible initial properties that could be easily tailored by adjusting either the number of sprayed layers and/or the solution composition. The selectivity of QRS was varied by changing the chemical nature of the polymer matrix in which carbon nanotubes (CNTs) were dispersed in solution, i.e., poly(carbonate) (PC), poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(styrene) (PS), and poly(methyl methacrylate) (PMMA). The e-nose was then successfully used to detect several volatile organic compounds (VOCs) selected among lung cancer biomarkers: a first set of seven polar vapours (water, ethanol, methanol, acetone, propanol, isopropanol, and 2-butanone), and another set of eleven less and nonpolar vapours (chloroform, toluene, benzene, styrene, cyclohexane, o-xylene, n-propane, n-decane, 1,2,4-trimethyl benzene, isoprene, and 1-hexene). The discrimination ability of the e-nose evaluated after a 3D principal component analysis (PCA) pattern recognition treatment was proved to be very good. Moreover, the quantitativity of the transducers' chemo-resistive responses was well fitted with the Langmuir-Henry-Clustering (LHC) model for both acetone and toluene vapours in a wide range of concentrations. The QRS developed in this study appear to be very good candidates to design low cost e-noses for the anticipated diagnosis of lung cancer by VOC analysis in breath, with ppm level sensitivity (tested down to 2.5 parts per million), short response time (a couple of seconds), low consumption, and a large signal to noise ratio (SNR >/= 10).

Chen, C., et al. (2010). "Quantum-dot-based immunofluorescent imaging of HER2 and ER provides new insights into breast cancer heterogeneity." Nanotechnology **21**(9): 095101.

Breast cancer (BC) is a heterogeneous tumor, and better understanding of its heterogeneity is essential to improving treatment effect. Quantum dot (QD)-based immunofluorescent nanotechnology (QD-IHC) for molecular pathology has potential advantages in delineating tumor heterogeneity. This potential is explored in this paper by QD-IHC imaging of HER2 and ER. BC heterogeneity can be displayed more clearly and sensitively by QD-IHC than conventional IHC in BC tissue microarrays. Furthermore, the simultaneous imaging of ER and HER2 might help understand their interactions during the process of evolution of heterogeneous BC.

Chen, C., et al. (2009). "Quantum dots-based immunofluorescence technology for the quantitative determination of HER2 expression in breast cancer." Biomaterials **30**(15): 2912-2918.

HER2 detection is important for breast cancer (BC) treatment and prognosis, but the detection methods currently used have some disadvantages. Quantum dots (QDs)-based probes provide a potentially important new method for HER2 detection in clinical practice. This potential is examined in this paper. A QDs HER2 probe kit and QDs image acquisition and analysis software were developed and applied to 94 clinical samples of BC. Compared to conventional immunohistochemistry techniques, this method provided a superior accurate and sensitive method for the detection of HER2 in clinical breast cancer diagnosis.

Chen, C., et al. (2011). "Quantum dots-based molecular classification of breast cancer by quantitative spectroanalysis of hormone receptors and HER2." Biomaterials **32**(30): 7592-7599.

The emerging molecular breast cancer (BC) classification based on key molecules, including hormone receptors (HRs), and human epidermal growth factor receptor 2 (HER2) has been playing an important part of clinical practice guideline. The current molecular classification mainly based on their fingerprints, however, could not provide enough essential information for treatment decision making. The

molecular information on both patterns and quantities could be more helpful to heterogeneities understanding for BC personalized medicine. Here we conduct quantitative determination of HRs and HER2 by quantum dots (QDs)-based quantitative spectral analysis, which had excellent consistence with traditional method. Moreover, we establish a new molecular classification system of BC by integrating the quantitative information of HER2 and HRs, which could better reveal BC heterogeneity and identify 5 molecular subtypes with different 5-year prognosis. Furthermore, the emerging 5 molecular subtypes based on simple quantitative molecules information could be as informative as multi-genes analysis in routine practice, and might help formulate a more personalized comprehensive therapy strategy and prognosis prediction.

Chen, C., et al. (2010). "The quantitative detection of total HER2 load by quantum dots and the identification of a new subtype of breast cancer with different 5-year prognosis." Biomaterials **31**(33): 8818-8825.

Accurate classification is fundamental for breast cancer (BC) personalized care. Current BC classification based on the either traditional morphological staging or molecular signatures seems inefficient to reveal the"true"behaviors of invasive BC evolution. An appropriate approach combining the macro- and micro-pathologic information might be more useful academically as well as clinically. Here we explore a holistic approach by integrating a key molecular prognostic indicator of BC, HER2, with quantitative determination using quantum dots (QDs)--based nanotechnology and spectral analysis, and a key macropathologic indicator, tumor size, resulting a new indicator, total HER2 load. This indicator might better reveal BC heterogeneity and new subtypes of BC with different 5-year disease-free survival compared with current methods, which could be helpful in formulating a more personalized targeted therapy for BC. Furthermore, this mode integrating macro- and micro-pathological indicators might help gain new insights into invasive BC biological behaviors.

Chen, C. T., et al. (2021). "Fluorescent Nanohybrids from ZnS/CdSe Quantum Dots Functionalized with Triantennary, N-Hydroxy-p-(4-arylbutanamido)benzamide/Gallamide Dendrons That Act as Inhibitors of Histone Deacetylase for Lung Cancer." ACS Appl Bio Mater **4**(3): 2475-2489.

N-Hydroxy-p-(4-arylbutanamido)benzamides (HABAB) belong to one class of histone deacetylase inhibitors (HDACi), which regulate deacetylation of lysine residue's amino group in histone, which results in chromatin constriction. In addition, transcriptional knockdown of the genetic loci possessing the suppressor genes of tumor occurs. A tripodal, HABAB-capped gallamide dendron possessing thiol anchoring unit was prepared by the click method. The resultant hydrophilic dendritic unit was easily attached on the outer layer of CdSe/ZnS (i.e., core/shell type) quantum dots by thiolate-Zn interaction, as supported via (1)H NMR spectroscopic analysis of the conjugate with its original property of fluorescence. The resulting, water-miscible nanohybrid (nano-HTPB) which bore trivalent, peripheral HABABs as the HDACi was efficiently taken up by cells of lung cancer and transported into the nuclei of cells in 3 h, as confirmed by confocal microscopy analysis. The concentration levels of 50% inhibition (IC50) after 48 h incubation of the nano-HTPB for A549 and H1299 lung cancer cell lines were 14 and 18 nM, respectively, which were about 150-fold lower than those of the parent HTPB analogues. Nano-HTPB at 20 nM induced the knockdown of cell cycle at second growth/mitosis (i.e., G2/M) transition, which eventually led to apoptosis of lung cancer cells, demonstrating that the nano-HTPB was much more potent in inhibiting lung cancer cell growth in a synergistic manner than the parent HTPB analogues. In addition, the dendritic HABAB-capped nanohybrid, nano-HTPB, is more effective than the parent HTPB analogues both in vitro and in vivo. Furthermore, the nano-HTPB is more effective than the parent HTPB to increase the acetylation level of proteins related to histone and nonhistone like p53 and tubulin. Our results confirmed that covalent encapsulation of quantum dots with peripheral, triantennary HDACis represented a feasible strategy for synergistic drug delivery with enhanced biological effects.

Chen, D., et al. (2021). "Selective mediation of ovarian cancer SKOV3 cells death by pristine carbon quantum dots/Cu2O composite through targeting matrix metalloproteinases, angiogenic cytokines and cytoskeleton." J Nanobiotechnology **19**(1): 68.

It was shown that some nanomaterials may have anticancer properties, but lack of selectivity is one of challenges, let alone selective suppression of cancer growth by regulating the cellular microenvironment. Herein, we demonstrated for the first time that carbon quantum dots/Cu2O composite (CQDs/Cu2O) selectively inhibited ovarian cancer SKOV3 cells by targeting cellular microenvironment, such as matrix metalloproteinases, angiogenic cytokines and cytoskeleton. The result was showed CQDs/Cu2O possessed anticancer properties against SKOV3 cells with IC50 = 0.85 mug mL(-1), which was approximately threefold lower than other tested cancer cells and approximately 12-fold lower than normal cells. Compared with popular anticancer drugs, the IC50 of CQDs/Cu2O was approximately 114-fold and 75-fold lower than the IC50 of commercial artesunate (ART)

and oxaliplatin (OXA). Furthermore, CQDs/Cu2O possessed the ability to decrease the expression of MMP-2/9 and induced alterations in the cytoskeleton of SKOV3 cells by disruption of F-actin. It also exhibited stronger antiangiogenic effects than commercial antiangiogenic inhibitor (SU5416) through down-regulating the expression of VEGFR2. In addition, CQDs/Cu2O has a vital function on transcriptional regulation of multiple genes in SKOV3 cells, where 495 genes were up-regulated and 756 genes were down-regulated. It is worth noting that CQDs/Cu2O also regulated angiogenesis-related genes in SKOV3 cells, such as Maspin and TSP1 gene, to suppress angiogenesis. Therefore, CQDs/Cu2O selectively mediated of ovarian cancer SKOV3 cells death mainly through decreasing the expression of MMP-2, MMP-9, F-actin, and VEGFR2, meanwhile CQDs/Cu2O caused apoptosis of SKOV3 via S phase cell cycle arrest. These findings reveal a new application for the use of CQDs/Cu2O composite as potential therapeutic interventions in ovarian cancer SKOV3 cells.

Chen, H., et al. (2014). "Characterization of tumor-targeting Ag2S quantum dots for cancer imaging and therapy in vivo." Nanoscale **6**(21): 12580-12590.

Nanomedicine platforms that have the potential to simultaneously provide the function of molecular imaging and therapeutic treatment in one system are beneficial to address the challenges of cancer heterogeneity and adaptive resistance. In this study, Cyclic RGD peptide (cRGD), a less-expensive active tumor targeting tri-peptide, and doxorubicin (DOX), a widely used chemotherapeutic drug, were covalently attached to Ag2S quantum dots (QDs) to form the nano-conjugates Ag2S-DOX-cRGD. The optical characterization of Ag2S-DOX-cRGD manifested the maintenance of QDs fluorescence, which suggested the potential of Ag2S for monitoring intracellular and systemic drug distribution. The low biotoxicity of Ag2S QDs indicated that they are promisingly safe nanoparticles for bio-applications. Furthermore, the selective imaging and favorable tumor inhibition of the nanoconjugates were demonstrated at both cell and animal levels. These results indicated a promising future for the utilization of Ag2S QDs as a kind of multi-functional nano platform to achieve imaging-visible nano-therapeutics.

Chen, H., et al. (2021). "Redox responsive nanoparticle encapsulating black phosphorus quantum dots for cancer theranostics." Bioact Mater **6**(3): 655-665.

Effective cancer treatment puts high demands for cancer theranostics. For cancer diagnostics, optical coherence tomography (OCT) technology (including photothermal optical coherence tomography (PT-OCT)) has been widely investigated since it induces changes in optical phase transitions in tissue through environmental changes (such as temperature change for PT-OCT). In this report, redox responsive nanoparticle encapsulating black phosphorus quantum dots was developed as a robust PT-OCT agent. Briefly, black phosphorus quantum dots (BPQDs) are incorporated into cysteine-based poly-(disulfide amide) (Cys-PDSA) to form stable and biodegradable nanoagent. The excellent photothermal feature allows BPQD/Cys-PDSA nanoparticles (NPs) as a novel contrast agent for high-resolution PT-OCT bioimaging. The Cys-PDSA can rapidly respond to glutathione and effectively release BPQDs and drugs in vitro and in vivo. And the obtained NPs exhibit excellent near-infrared (NIR) photothermal transduction efficiency and drug delivery capacity that can serve as novel therapeutic platform, with very low chemo drug dosage and side effects. Both of the polymer and BPQD are degradable, indicating this platform is a rare PT-OCT agent that is completely biodegradable. Overall, our research highlights a biodegradable and biocompatible black phosphorus-based nanoagent for both cancer diagnosis and therapy.

Chen, H., et al. (2017). "Effects of surface modification of quantum dots on viability and migration of triple-negative breast cancer cells." J Colloid Interface Sci **485**: 51-58.

Triple-negative breast cancer (BC) shows strong metastasis and has a bad prognosis. There are few effective approaches until date to detect BC cells at an early stage. Quantum dots (QDs) are one of the most promising nanomaterials for the detection of BC cells. QDs are usually modified with some functional molecules, such as PEG and BSA, to decrease or possibly eliminate their toxicity. Although a large number of studies have investigated the cytotoxicity of QDs, the effects of surface modification of QDs on biological behaviors of triple-negative BC cells remain unclear. In this work, QDs were prepared using the hydrothermal method and chemically modified with PEG and BSA. The optical performance of QDs was recorded with a digital camera. Their absorption and fluorescence (FL) properties were analyzed by UV-Vis spectrometer and FL spectrophotometer, respectively. The effects of QDs and surface modification on viability and migration were principally investigated. The possible mechanism was primarily analyzed. The results show that QDs exhibit excellent optical performance under ultraviolet irradiation. Surface modification slightly reduces the photon count reaching the QDs surface. Moreover, surface modification results in a blue-shift of FL peak of QDs, which is ascribed to the change in surface chemical environment because of PEG and BSA modifications. In addition, QDs, PEG coated QDs (PEG@CdTe) and BSA coated QDs (BSA@CdTe) can reduce viability and inhibit migration

of BC cells. The inhibition effects are time- and concentration-dependent. In addition, PEG and BSA modified QDs exhibit lower inhibition effects on BC cells, as compared with unmodified QDs. In this process, Reactive oxygen species (ROS) does not appear to play an important role, and other pathways should be considered. This work provides experimental support and useful clinical guidance for QDs-applications in BC detection.

Chen, H., et al. (2009). "Comparison of quantum dots immunofluorescence histochemistry and conventional immunohistochemistry for the detection of caveolin-1 and PCNA in the lung cancer tissue microarray." J Mol Histol **40**(4): 261-268.

Luminescent semiconductor quantum dots (QDs) are a new class of fluorescent label with wide ranges of applications in cell imaging. In this study, we evaluated the capability of QDs immunofluorescence histochemistry (QDs-IHC) for detecting antigens of caveolin-1 and PCNA in the lung cancer tissue microarray (TMA) in comparison with the conventional immunohistochemistry (IHC) technique. Both methods revealed consistent antigen localization and statistically non-significant detection rates of caveolin-1 and PCNA expressions in our study. However, the sensitivity of QDs-IHC was higher than IHC. The positive detection rates of caveolin-1 and PCNA by QDs-IHC were 57% (40/70) and 86% (60/70), respectively, which were higher than the detection rates of 47% (33/70) and 77% (54/70), respectively, by IHC. Moreover, QDs exhibited a much better photostability, a broader excitation spectrum and a longer fluorescence lifetime. We showed here the advantages of QDs-IHC over IHC for the detection of caveolin-1 and PCNA in lung cancer TMA.

Chen, H. L., et al. (2009). "[Significance of caveolin-1 protein detected by quantum dots technique in human lung cancer invasiveness and metastasis.]." Zhonghua Jie He He Hu Xi Za Zhi **32**(11): 821-824.

OBJECTIVE: Fluorescent semiconductor nanocrystals [also known as quantum dots (QDs)] are nanometer-sized light-emitting particles and are emerging as a new class of fluorescent probes for cancer detection, due to their unique optical and electronic properties. The aim of this study was to investigate the expression of caveolin-1 (Cav-1), extracellular matrix metalloproteinase inducer (CD(147)/EMMPRIN), matrix metalloproteinase-2 (MMP-2) proteins in the human lung cancer tissue microarray (TMA) by QDs immunofluorescence histochemistry (QDs-IHC) and therefore to evaluate the relationship between Cav-1 protein and lung cancer invasiveness and metastasis. METHODS: QDs-IHC combined with TMA were used to detect the expression of Cav-1, CD(147) and MMP-2 proteins in 70 cases of human lung cancers and 5 cases of noncancerous lung tissues. RESULTS: The average immunofluorescence intensity of Cav-1 protein in the lung cancer group was 55 +/- 23, significantly lower than that in the control group (80 +/- 4, t = 2.461, P = 0.016). The expression of Cav-1 was not associated with the age and the gender of the patients, nor with the histology type of lung cancer (P > 0.05). The average immunofluorescence intensity of Cav-1 protein was associated significantly with TNM staging (t = 2.466, P = 0.016) and lymph node metastasis (t = 2.972, P = 0.004). A negative correlation was observed between Cav-1 and CD(147) protein expression (r = -0.331, P = 0.005), but no correlation was observed between Cav-1 and MMP-2 protein expression (P = 0.193). CONCLUSIONS: QDs-IHC could accurately and quantitatively detect different protein location in lung cancer TMA. A close relationship was detected between Cav-1 protein and the development of lung cancer. High expression of Cav-1 may be involved in invasiveness and metastasis of lung cancer, possibly through the regulation of CD(147) rather than MMP-2 activition.

Chen, J. Y., et al. (2010). "Quantum dot-mediated photoproduction of reactive oxygen species for cancer cell annihilation." Photochem Photobiol **86**(2): 431-437.

While semiconductor quantum dots produce little singlet oxygen, they may undergo Type I photoreactions to produce other reactive oxygen species (ROS) to kill cells. CdTe quantum dots coated with thioglycolic acid were used to test that possibility. Some thiol ligands were purposely removed to regenerate the surface electron traps that were passivated by the ligand. This allowed photoinduced electrons to dwell on the surface long enough to be gathered by nearby oxygen molecules to produce ROS. The photocytotoxicity of these quantum dots was tested on nasopharyngeal carcinoma cells. Photokilling was shown to be drug and light dose dependent. Using 0.6 mum quantum dots for incubation and 4.8 J cm(-2) for irradiation, about 80% of the cells were annihilated. These quantum dots promised to be potent sensitizers for photoannihilation of cancer cells.

Chen, L. D., et al. (2006). "[Quantum dots and their applications in cancer research]." Ai Zheng **25**(5): 651-656.

Quantum dots are semiconductor nanocrystals with physical dimensions smaller than the exciton Bohr radius. As their fluorescence emissions are size-tunable, we can acquire any spectrum from ultraviolet (UV) to near-infrared by changing the particles' radiuses. The large Stokes shifts of quantum dots can be used to further improve detection sensitivity. The luminescence intensity is high and stable. Single quantum dots have longer excited state lifetimes, and they appear 10-20 times brighter than organic fluorescent dyes. And they

have good biocompatibility because quantum dots with appropriate shells don't interfere with physiological processes, such as growth, development, signaling and motility. With the development of optical labeling and imaging technology, many present conventional biomedical methods have limitations in microcosmic direct real-time researches of bio-molecular interactions and early diagnosis of malignant tumors. The invention of quantum dots and their biomedical applications make them as good markers for tumor cell tracing and targeting in cancer research, such as prostate cancer, mammary cancer, cervical cancer, basal cell carcinoma, liver cancer, and melanoma. The current research is focused on tumor markers imaging and molecular interaction based on tangible carriers such as cells and tissues. The next research orientation would be to tap the potential of this highly sensitive technology to image tumor biomarkers in serum and other body fluids, so as to increase the early diagnosis rate of malignant tumors.

Chen, L. L., et al. (2022). "Near-Infrared-II Quantum Dots for In Vivo Imaging and Cancer Therapy." Small **18**(8): e2104567.

In vivo fluorescence imaging can perform real-time, noninvasive, and high spatiotemporal resolution imaging to accurately obtain the dynamic biological information in vivo, which plays significant roles in the early diagnosis and treatment of cancer. However, traditional in vivo fluorescence imaging usually operates in the visible and near-infrared (NIR)-I windows, which are severely interfered by the strong tissue absorption, tissue scattering, and autofluorescence. The emergence of NIR-II imaging at 1000-1700 nm significantly breaks through the imaging limitations in deep tissues, due to less tissue scattering and absorption. Benefiting from the outstanding optical properties of NIR-II quantum dots (QDs), such as high brightness and good photostability, in vivo fluorescence imaging exhibits excellent temporal-spatial resolution and large penetration depth, and QDs have become a kind of promising fluorescent biomarkers in the field of in vivo fluorescence imaging. Herein, the authors review NIR-II QDs from preparation to modification, and summarize recent applications of NIR-II QDs, including in vivo imaging and imaging-guided therapies. Finally, they discuss the special concerns when NIR-II QDs are shifted from in vivo imaging applications to further in-depth applications.

Chen, M. L., et al. (2012). "Quantum dots conjugated with Fe3O4-filled carbon nanotubes for cancer-targeted imaging and magnetically guided drug delivery." Langmuir **28**(47): 16469-16476.

A novel and specific nanoplatform for in vitro simultaneous cancer-targeted optical imaging and magnetically guided drug delivery is developed by conjugating CdTe quantum dots with Fe(3)O(4)-filled carbon nanotubes (CNTs) for the first time. Fe(3)O(4) is filled into the interior of the CNTs, which facilitates magnetically guided delivery and improves the synergetic targeting efficiency. In comparison with that immobilized on the external surface of CNTs, the magnetite nanocrystals inside the CNTs protect it from agglomeration, enhance its chemical stability, and improve the drug loading capacity. It also avoids magnetic nanocrystals-induced quenching of fluorescence of the quantum dots. The SiO(2)-coated quantum dots (HQDs) attached on the surface of CNTs exhibit favorable fluorescence as the hybrid SiO(2) shells on the QDs surface prevent its fluorescence quenching caused by the CNTs. In addition, the hybrid SiO(2) shells also mitigate the toxicity of the CdTe QDs. By coating transferrin on the surface of the herein modified CNTs, it provides a dual-targeted drug delivery system to transport the doxorubicin hydrochloride (DOX) into Hela cells by means of an external magnetic field. The nanocarrier based on the multifunctional nanoplatform exhibits an excellent drug loading capability of ca. 110%, in addition to cancer-targeted optical imaging as well as magnetically guided drug delivery.

Chen, M. L., et al. (2013). "Quantum-dot-conjugated graphene as a probe for simultaneous cancer-targeted fluorescent imaging, tracking, and monitoring drug delivery." Bioconjug Chem **24**(3): 387-397.

We report a novel quantum-dot-conjugated graphene, i.e., hybrid SiO2-coated quantum dots (HQDs)-conjugated graphene, for targeted cancer fluorescent imaging, tracking, and monitoring drug delivery, as well as cancer therapy. The hybrid SiO2 shells on the surface of QDs not only mitigate its toxicity, but also protect its fluorescence from being quenched by graphene. By functionalizing the surface of HQDs-conjugated graphene (graphene-HQDs) with transferrin (Trf), we developed a targeted imaging system capable of differential uptake and imaging of cancer cells that express the Trf receptor. The widely used fluorescent antineoplastic anthracycline drug, doxorubicin (DOX), is adsorbed on the surface of graphene and results in a large loading capacity of 1.4 mg mg(-1). It is advantageous that the new delivery system exhibits different fluorescence color in between graphene-HQDs and DOX in the aqueous core upon excitation at a same wavelength for the purpose of tracking and monitoring drug delivery. This simple multifunctional nanoparticle system can deliver DOX to the targeted cancer cells and enable us to localize the graphene-HQDs and monitor intracellular DOX release. The specificity and safety of the nanoparticle conjugate for cancer imaging, monitoring, and therapy has been demonstrated in vitro.

Choi, A. O., et al. (2008). "Quantum dot-induced epigenetic and genotoxic changes in human breast cancer cells." J Mol Med (Berl) **86**(3): 291-302.

The staggering array of nanotechnological products, found in our environment and those applicable in medicine, has stimulated a growing interest in examining their long-term impact on genetic and epigenetic processes. We examined here the epigenomic and genotoxic response to cadmium telluride quantum dots (QDs) in human breast carcinoma cells. QD treatment induced global hypoacetylation implying a global epigenomic response. The ubiquitous responder to genotoxic stress, p53, was activated by QD challenge resulting in translocation of p53, with subsequent upregulation of downstream targets Puma and Noxa. Consequential decrease in cell viability was in part prevented by the p53 inhibitor pifithrin-alpha, suggesting that p53 translocation contributes to QD-induced cytotoxicity. These findings suggest three levels of nanoparticle-induced cellular changes: non-genomic, genomic and epigenetic. Epigenetic changes may have long-term effects on gene expression programming long after the initial signal has been removed, and if these changes remain undetected, it could lead to long-term untoward effects in biological systems. These studies suggest that aside from genotoxic effects, nanoparticles could cause more subtle epigenetic changes which merit thorough examination of environmental nanoparticles and novel candidate nanomaterials for medical applications.

Choi, S. Y., et al. (2017). "Synthesis of upconversion nanoparticles conjugated with graphene oxide quantum dots and their use against cancer cell imaging and photodynamic therapy." Biosens Bioelectron **93**: 267-273.

Multifunctional nanocomposite has a huge potential for cell imaging, drug delivery, and improving therapeutic effect with less side effects. To date, diverse approaches have been demonstrated to endow a single nanostructure with multifunctionality. Herein, we report the synthesis and application of core-shell nanoparticles composed with upconversion nanoparticle (UCNP) as a core and a graphene oxide quantum dot (GOQD) as a shell. The UCNP was prepared and applied for imaging-guided analyses of upconversion luminescence. GOQD was prepared and employed as promising drug delivery vehicles to improve anti-tumor therapy effect in this study. Unique properties of UCNPs and GOQDs were incorporated into a single nanostructure to provide desirable functions for cell imaging and drug delivery. In addition, hypocrellin A (HA) was loaded on GOQDs for photo-dynamic therapy (PDT). HA, a commonly used chemotherapy drug and a photo-sensitizer, was conjugated with GOQD by pi-pi interaction and loaded on PEGylated UCNP without complicated synthetic process, which can break structure of HA. Applying these core-shell nanoparticles to MTT assay, we demonstrated that the UCNPs with GOQD shell loaded with HA could be excellent candidates as multifunctional agents for cell imaging, drug delivery and cell therapy.

Chou, K. L., et al. (2013). "Femto-second laser beam with a low power density achieved a two-photon photodynamic cancer therapy with quantum dots." J Mater Chem B **1**(36): 4584-4592.

Focusing the femto-second (fs) laser beam on the target was the usual way to carry out a two-photon excitation (TPE) in previous photodynamic therapy (PDT) studies. However, focusing the laser deep inside the tissues of the tumor is unrealistic due to tissue scattering, so that this focusing manner seems unfit for practical TPE PDT applications. In this work, we prepared a conjugate of quantum dots (QDs) and sulfonated aluminum phthalocyanine (AlPcS) for TPE PDT, because QDs have a very high two-photon absorption cross section (TPACS) and thus QDs can be excited by an unfocused 800 nm fs laser beam with a low power density and then transfer the energy to a conjugated AlPcS via fluorescence resonance energy transfer (FRET). The FRET efficiency of the QD-AlPcS conjugate in water was as high as 90%, and the FRET process of the cellular QD-AlPcS was also observed in both KB and HeLa cells under TPE of a 800 nm fs laser. The singlet oxygen ((1)O2) products were produced by the QD-AlPcS under the TPE of the unfocused 800 nm fs laser via FRET mediated PDT. Moreover, the QD-AlPcS can effectively destroy these cancer cells under the irradiation of the 800 nm unfocused fs laser beam with a power density of 92 mW mm(-2), and particularly the killing efficiency of the TPE is comparable to that of the commonly used one-photon excitation (OPE) at visible wavelengths. These results highlight the potential of QD-AlPcS for TPE PDT with a near infrared wavelength.

Chu, M., et al. (2012). "The therapeutic efficacy of CdTe and CdSe quantum dots for photothermal cancer therapy." Biomaterials **33**(29): 7071-7083.

Fluorescent quantum dots (QDs) used for biomedical imaging and diagnostics have attracted considerable attention over the past decade. Here, we report our finding regarding the therapeutic efficacy of the popularly used red/brown, brown or close to black CdTe and CdSe QDs. Upon 671-nm laser irradiation, these QDs can rapidly convert light energy into heat, both in vitro and in vivo. In the present study, the growth of mouse melanoma tumors injected with CdTe(710) QDs coated with a silica shell (SiO(2)) was significantly inhibited after laser irradiation, with eventual

disappearance of the tumor. In contrast, tumors injected with the silica-coated QDs without subsequent irradiation continued to grow over time. They had a growth rate close to that of tumors injected with SiO(2) or phosphate-buffered saline, with or without laser irradiation. In conclusion, our data suggest that the popularly used CdTe and CdSe QDs have great potential in the treatment of cancer using photothermal therapy.

Ciarlo, M., et al. (2009). "Use of the semiconductor nanotechnologies "quantum dots" for in vivo cancer imaging." Recent Pat Anticancer Drug Discov **4**(3): 207-215.

Non-invasive in vivo imaging offers great potential to facilitate translational drug development research at the animal testing phase. The emerging luminescent nanoparticles or quantum dots provide a new type of biological agents that can improve these applications. The advantages of luminescent nanoparticles for biological applications include their high quantum yield, color availability, good photo-stability, large surface-to-volume ratio, surface functionality, and small size. These properties could improve the sensitivity of biological detection and imaging by at least 10- to 100-fold and make them an exceptional tool for live-cell imaging. In this review patents on applications of semiconductor quantum dots for in vivo imaging are discussed.

Cooper, W. G. (1993). "Roles of evolution, quantum mechanics and point mutations in origins of cancer." Cancer Biochem Biophys **13**(3): 147-170.

The fact point genetic lesions--which provide the species with an ability to respond favorably to changing environmental conditions--are also specifically compatible with "activating" point mutation sensitive, evolutionarily conserved proto-oncogenes and gene p53 implies an additional function for evolutionary processes. In particular, this suggests that evolutionary point lesions may also be designed to remove from the gene pool those genomes which have accumulated advanced levels of evolutionary-induced mutations, thereby protecting the species from the adverse consequences of accumulating mutations beyond an unsafe upper limit. This hypothesis is used to construct a mutation model polynomial for incidence of human cancer as a function of age. The model assumes that point lesion sensitive proto-oncogenes and "p53-type" genes are evolutionarily conserved and must exhibit wild-type genetic information at fertilization for proper growth. Subsequently, evolutionary lesions populate these conserved domains, eventually causing point lesion sensitive genes to yield amino acid substituted proteins capable of participation in transforming normal cells to cancer. The mechanism for evolutionary base substitutions is a time-dependent Topal-Fresco process in which the required unusual tautomers are provided by proton exchange tunneling (see, W.G. Cooper, 1992a). The very good agreement between incidence of cancer data and the model is consistent with the hypothesis that duplex DNA has been evolutionarily designed to supplying an optimum rate of point mutation variation for purposes of (a) providing the species with the ability to respond favorably to changing environmental conditions and (b) to protect the species from adverse consequences of accumulating excessive mutations. (e.g., W.G. Cooper, 1992b). As a result of identifying "tunneling sensitive" DNA codes, consequences of evolutionary lesions in diploid and haploid human genomes are evaluated. The "faster evolving" oocyte genome may be responsible for most evolutionary traits, whereas evolutionarily conserved domains may be supplied by the "slower evolving" male haploid genome. Evidence from fragile X genetic systems support this conclusion. The model further illustrates how fragile X genetic properties could be a result of evolutionary lesions altering genetic specificities of "tunneling sensitive" CGG codes to specify DNA synthesis initiation codons, CUG or UUG. This could cause reinitiation of DNA synthesis and the addition of more CGG codes to the "tunneling sensitive" segment of consecutive (CGG)n repeats which would explain how (CGG)n segments are "expanded" during oogenesis.

Cunci, L., et al. (2021). "Multicolor Fluorescent Graphene Oxide Quantum Dots for Sensing Cancer Cell Biomarkers." ACS Appl Nano Mater **4**(1): 211-219.

Onion-like carbon nanoparticles were synthesized from diamond nanoparticles to be used as the precursor for graphene oxide quantum dots. Onion-like carbon nanoparticles were exfoliated to produce two types of nanoparticles, graphene oxide quantum dots that showed size-dependent fluorescence and highly stable inner cores. Multicolor fluorescent quantum dots were obtained and characterized using different techniques. Polyacrylamide gel electrophoresis showed a range of emission wavelengths spanning from red to blue with the highest intensity shown by green fluorescence. Using high-resolution transmission electron microscopy, we calculated a unit cell size of 2.47 A in a highly oxidized and defected structure of graphene oxide. A diameter of ca. 4 nm and radius of gyration of ca. 11 A were calculated using small-angle X-ray scattering. Finally, the change in fluorescence of the quantum dots was studied when single-stranded DNA that is recognized by telomerase was attached to the quantum dots. Their interaction with the telomerase present in cancer cells was observed and a change was seen after six days, providing an important application of these modified graphene oxide quantum dots for cancer sensing.

Das, P. and U. J. Krull (2017). "Detection of a cancer biomarker protein on modified cellulose paper by fluorescence using aptamer-linked quantum dots." Analyst **142**(17): 3132-3135.

The development of point-of-care bioassays for sensitive screening of protein-based cancer biomarkers would improve the opportunity for early stage diagnosis. A strategy for a fluorescence resonance energy transfer (FRET)-based bioassay has been investigated that makes use of modified cellulose paper for the detection of an epithelial cell adhesion molecule (EpCAM), which is a transmembrane glycoprotein that is overexpressed in several tumors of epithelial origin. The paper matrix was a substrate for immobilized aptamer-linked quantum dots (QDs-Apt) and Cy3 labeled complementary DNA (cDNA), which served as a donor and an acceptor, respectively. Competitive binding of EpCAM displaced the cDNA, resulting in the reduction of FRET. The paper-based bioassay was able to detect EpCAM in buffer solution as well as in 10% bovine serum solution using a reaction time of no more than 60 minutes. The dynamic range was 1-100 nM in buffer with a precision better than 4%, and the limit of detection was 250 pM in buffer and 600 pM in 10% serum.

Das, R. K. and S. Mohapatra (2017). "Highly luminescent, heteroatom-doped carbon quantum dots for ultrasensitive sensing of glucosamine and targeted imaging of liver cancer cells." J Mater Chem B **5**(11): 2190-2197.

A novel fluorescent boronate nanoprobe has been synthesized by judiciously doping boron, nitrogen, and sulphur in carbon quantum dots (BNSCQD). Specifically, the synergistic presence of nitrogen and sulphur along with boronic acid provides excellent luminescence properties and offers recognition sites for specific sensing of glucosamine. Fluorescence intensity enhances in the presence of glucosamine because of agglomeration of luminescent centers, and thus restricts nonradiative emission channels. The detection limit of this turn on fluorescence for glucosamine is 0.7 nM in PBS. Following this protocol, for the first time, a paper based sensor strip has been prepared for naked eye detection of glucosamine with an LOD of 2.5 muM. The developed nanoprobe shows very low cytotoxicity. More interestingly, boronic acid located on the surface of BNSCQD offers molecular recognition sites for the sialyl Lewis(a) receptor, which is overexpressed on the surface of liver cancer cells (HepG2). The selective uptake of the BNSCQD nanoprobe in HepG2 cells compared to L929, 3T3 and PC3 cells shows its cell targeting capability.

Das, R. K., et al. (2019). "N-Doped Carbon Quantum Dot (NCQD)-Deposited Carbon Capsules for Synergistic Fluorescence Imaging and Photothermal Therapy of Oral Cancer." Langmuir **35**(47): 15320-15329.

Use of nanomaterials blessed with both therapeutic and diagnostic properties is a proficient strategy in the treatment of cancer in its early stage. In this context, our paper reports the synthesis of uniform size N-rich mesoporous carbon nanospheres of size 65-70 nm from pyrrole and aniline precursors using Triton-X as a structure-directing agent. Transmission electron microscopy reveals that these carbons spheres contain void spaces in which ultrasmall nitrogen-doped quantum dots (NCQD) are captured within the matrix. These mesoporous hollow NCQD captured carbon spheres (NCQD-HCS) show fluorescence quantum yield up to 14.6% under lambdaex = 340 nm. Interestingly, samples calcined at >800 degrees C clearly absorb in the wavelength range 700-1000 nm and shows light-to-heat conversion efficiency up to 52%. In vitro experiments in human oral cancer cells (FaDu) show that NCQD-HCS are internalized by the cells and induce a substantial thermal ablation effect in FaDu cells when exposed under a 980 nm near-infrared laser.

Davies, P., et al. (2012). "Implications of quantum metabolism and natural selection for the origin of cancer cells and tumor progression." AIP Adv **2**(1): 11101.

Empirical studies give increased support for the hypothesis that the sporadic form of cancer is an age-related metabolic disease characterized by: (a) metabolic dysregulation with random abnormalities in mitochondrial DNA, and (b) metabolic alteration - the compensatory upregulation of glycolysis to offset mitochondrial impairments. This paper appeals to the theory of Quantum Metabolism and the principles of natural selection to formulate a conceptual framework for a quantitative analysis of the origin and proliferation of the disease. Quantum Metabolism, an analytical theory of energy transduction in cells inspired by the methodology of the quantum theory of solids, elucidates the molecular basis for differences in metabolic rate between normal cells, utilizing predominantly oxidative phosphorylation, and cancer cells utilizing predominantly glycolysis. The principles of natural selection account for the outcome of competition between the two classes of cells. Quantum Metabolism and the principles of natural selection give an ontogenic and evolutionary rationale for cancer proliferation and furnish a framework for effective therapeutic strategies to impede the spread of the disease.

De, S., et al. (2018). "Tailoring the Efficacy of Multifunctional Biopolymeric Graphene Oxide Quantum Dot-Based Nanomaterial as Nanocargo in Cancer Therapeutic Application." ACS Biomater Sci Eng **4**(2): 514-531.

Nanotechnology has acquired an immense recognition in cancer theranostics. Considerable progress has been made in the development of targeted drug delivery system for potent delivery of anticancer drugs to tumor-specific sites. Recently, multifunctional nanomaterials have been explored and used as nanovehicles to carry drug molecules with enhanced therapeutic efficacy. In this present work, graphene oxide quantum dot (GOQD) was conjugated with folic acid functionalized chitosan (FA-CH) to develop a nanocargo (FA-CH-GOQD) for drug delivery in cancer therapy. The synthesized nanomaterials were characterized using Fourier transform infrared spectroscopy, ultraviolet-visible spectroscopy, scanning electron microscopy, transmission electron microscopy, and dynamic light scattering. Photoluminescence spectroscopy was also employed to characterize the formation of GOQD. To validate the efficacy of FA-CH-GOQD as nanocarriers, doxorubicin (DOX) drug was chosen for encapsulation. The in vitro release pattern of DOX was examined in various pH ranges. The drug release rate in a tumor cell microenvironment at pH 5.5 was found higher than that under a physiological range of pH 6.5 and 7.4. An MTT assay was performed to understand the cytotoxic behavior of GOQD and FA-CH-GOQD/DOX. Cytomorphological micrographs of the A549 cell exhibited the various morphological arrangements subject to apoptosis of the cell. Cellular uptake studies manifested that FA-CH-GOQD could specifically transport DOX within a cancerous cell. Further anticancer efficacy of this nanomaterial was corroborated in a breast cancer cell line and demonstrated through 4',6-diamidino-2-phenylindole dihydrochloride staining micrographs.

Demetrius, L. A., et al. (2010). "Cancer proliferation and therapy: the Warburg effect and quantum metabolism." Theor Biol Med Model **7**: 2.

BACKGROUND: Most cancer cells, in contrast to normal differentiated cells, rely on aerobic glycolysis instead of oxidative phosphorylation to generate metabolic energy, a phenomenon called the Warburg effect. MODEL: Quantum metabolism is an analytic theory of metabolic regulation which exploits the methodology of quantum mechanics to derive allometric rules relating cellular metabolic rate and cell size. This theory explains differences in the metabolic rates of cells utilizing OxPhos and cells utilizing glycolysis. This article appeals to an analytic relation between metabolic rate and evolutionary entropy - a demographic measure of Darwinian fitness - in order to: (a) provide an evolutionary rationale for the Warburg effect, and (b) propose methods based on entropic principles of natural selection for regulating the incidence of OxPhos and glycolysis in cancer cells. CONCLUSION: The regulatory interventions proposed on the basis of quantum metabolism have applications in therapeutic strategies to combat cancer. These procedures, based on metabolic regulation, are non-invasive, and complement the standard therapeutic methods involving radiation and chemotherapy.

Deng, M., et al. (2020). "Graphene quantum dots: efficient mechanosynthesis, white-light and broad linear excitation-dependent photoluminescence and growth inhibition of bladder cancer cells." Dalton Trans **49**(7): 2308-2316.

Heteroatom-doped graphene quantum dots (GQDs) have attracted considerable attention due to their potential applications as luminescent materials and in biology. In this work, we developed a solvent-free gram-scale mechanochemical method for the preparation of nitrogen-doped graphene quantum dots (N-GQDs) with the highest solubility (31 mg mL(-1)) in water reported to date. Commercial graphite was sheared and cut through grinding with solid melamine and then ground with solid KOH to get sub-5 nm-sized, 1-3-layered N-GQDs. Notably, these N-GQDs exhibit white-light emission and broad excitation-dependent full-color photoluminescence from 463 nm to 672 nm. When the excitation light ranged from 325 nm to 485 nm, these mechanochemically obtained N-GQDs exhibited bright white-light emission. Intriguingly, the change in the emission wavelength has two-stage linear relationships with the change in the excitation wavelength, and the inflection point is at 580 nm (excited at 550 nm). The difference between the emission and excitation wavelengths decreases from 138 to 12 nm, which also shows two-stage linear relationships with the change in the excitation wavelength. It is notable that their PL quantum yields are high, up to 26.6%. Furthermore, we studied the inhibitory effect of as-obtained N-GQDs on bladder cancer cells (UMUC-3); as a result, with the increase of the concentration of N-GQDs, the proliferation of cancer cells was obviously prohibited.

Desai, M. L., et al. (2019). "Influence of doping ion, capping agent and pH on the fluorescence properties of zinc sulfide quantum dots: Sensing of Cu(2+) and Hg(2+) ions and their biocompatibility with cancer and fungal cells." Spectrochim Acta A Mol Biomol Spectrosc **210**: 212-221.

Herein, a facile one-pot synthetic method was explored for the fabrication of glutathione capped Mn(2+) dopedzinc sulphide quantum dots (GSH-Mn(2+)-ZnS QDs) for both fluorescent detection of Cu(2+) and Hg(2+) ions and for fluorescence imaging of two cancer (RIN5F and MDAMB231) and fungal (Rhizopus oryzae) cells. Particularly, doping of Mn(2+) into ZnS QDs nanocrystal structure resulted a great improvement in the fluorescence properties of ZnS QDs.

The emission peak of undoped ZnS QDs was found at 447nm, which is due to the large number of surface defects in the ZnS QDs nanostructures. Under identical conditions, there is a good linear relationship between the quenching of fluorescence intensity and analytes (Cu(2+) and Hg(2+) ions) concentration in the range of 0.005 to 0.2mM and of 0.025 to 0.4mM for Cu(2+) and Hg(2+) ions, respectively. The GSH-Mn(2+)-ZnS QDs exhibit least cytotoxicity against RIN5F and MDAMB231 cells, demonstrating the multifunctional applications in sensing of metal ions and biocompatibility towards cancer (RIN5F and MDAMB231) and fungal (Rhizopus oryzae) cells.

Dhas, N., et al. (2022). "Organic quantum dots: An ultrasmall nanoplatform for cancer theranostics." J Control Release **348**: 798-824.

Tumours are the second leading cause of death globally, generating alterations in biological interactions and, as a result, malfunctioning of crucial genetic traits. Technological advancements have made it possible to identify tumours at the cellular level, making transcriptional gene variations and other genetic variables more easily investigated. Standard chemotherapy is seen as a non-specific treatment that has the potential to destroy healthy cells while also causing systemic toxicity in individuals. As a result, developing new technologies has become a pressing necessity. QDs are semiconductor particles with diameters ranging from 2 to 10 nanometers. QDs have grabbed the interest of many researchers due to their unique characteristics, including compact size, large surface area, surface charges, and precise targeting. QD-based drug carriers are well known among the many nanocarriers. Using QDs as a delivery approach enhances solubility, lengthens retention time, and reduces the harmful effects of loaded medicines. Several varieties of quantum dots used in drug administration are discussed in this article, along with their chemical and physical characteristics and manufacturing methods. Furthermore, it discusses the role of QDs in biological, medicinal, and theranostic applications.

Di Corato, R., et al. (2011). "Multifunctional nanobeads based on quantum dots and magnetic nanoparticles: synthesis and cancer cell targeting and sorting." ACS Nano **5**(2): 1109-1121.

Trifunctional polymer nanobeads are prepared by destabilization of a mixture of magnetic nanoparticles, quantum dots, and an amphiphilic polymer, followed by functionalization of the bead surface with folic acid molecules. The distribution of the nanoparticles within the nanobeads can be tuned using either acetonitrile or water as destabilizing solvent. The luminescence of the resulting beads can be tuned by varying the ratio of quantum dots per magnetic nanoparticles. The application of an external magnetic field (such as a small static magnet of 0.3 T) to the magnetic-fluorescent nanobeads allows the quantitative accumulation of the beads within a few hours depending on the total size of the beads. Furthermore, specific targeting of cancer cells overexpressing folate receptors is achieved thanks to the folic acid decorating the surface of the as-synthesized nanobeads. Folate receptor mediated cellular uptake of the folic acid-functionalized nanobeads is proven via both confocal imaging and transmission electron microscopy characterization. Cell sorting experiments performed with trifunctional nanobeads show quantitative recovering of targeted cells even when they are present at low percentage (up to 1%).

Ding, D., et al. (2017). "MoO3-x quantum dots for photoacoustic imaging guided photothermal/photodynamic cancer treatment." Nanoscale **9**(5): 2020-2029.

A theranostic system of image-guided phototherapy is considered as a potential technique for cancer treatment because of the ability to integrate diagnostics and therapies together, thus enhancing accuracy and visualization during the treatment. In this work, we realized photoacoustic (PA) imaging-guided photothermal (PT)/photodynamic (PD) combined cancer treatment just via a single material, MoO3-x quantum dots (QDs). Due to their strong NIR harvesting ability, MoO3-x QDs can convert incident light into hyperthermia and sensitize the formation of singlet oxygen synchronously as evidenced by in vitro assay, hence, they can behave as both PT and PD agents effectively and act as a "dual-punch" to cancer cells. In a further study, elimination of solid tumors from HeLa-tumor bearing mice could be achieved in a MoO3-x QD mediated phototherapeutic group without obvious lesions to the major organs. In addition, the desired PT effect also makes MoO3-x QDs an exogenous PA contrast agent for in vivo live-imaging to depict tumors. Compared with previously reported theranostic systems that put several components into one system, our multifunctional agent of MoO3-x QDs is exempt from unpredictable mutual interference between components and ease of leakage of virtual components from the composited system.

Ding, H., et al. (2017). "Beyond a Carrier: Graphene Quantum Dots as a Probe for Programmatically Monitoring Anti-Cancer Drug Delivery, Release, and Response." ACS Appl Mater Interfaces **9**(33): 27396-27401.

On the basis of the unique physicochemical properties of graphene quantum dots (GQDs), we developed a novel type of theranostic agent by loading anticancer drug doxorubicin (DOX) to GQD's surface

and conjugating Cy5.5 (Cy) dye to GQD though a cathepsin D-responsive (P) peptide. Such type of agents demonstrated superior therapeutic performance both in vitro and in vivo because of the improved tissue penetration and cellular uptake. More importantly, they are capable of functioning as probes for programmed tracking the delivery and release of anticancer drug as well as drug-induced cancer cell apoptosis through GQD's, DOX's, and Cy's charateristic fluorescence, respectively.

Dong, C. and J. Ren (2012). "Water-soluble mercaptoundecanoic acid (MUA)-coated CdTe quantum dots: one-step microwave synthesis, characterization and cancer cell imaging." Luminescence **27**(3): 199-203.

In this study, a one-step approach for aqueous synthesis of highly luminescent semiconductors, CdTe quantum dots (QDs), using long-chain thiols-mercaptoundecanoic acid (MUA) as surface ligand, was developed in a microwave irradiation system. The synthetic conditions were systematically investigated. The as-prepared MUA-coated QDs were characterized by various spectroscopy techniques, transmission electron microscopy (TEM) and X-ray powder diffraction (XRD). The experimental results document that MUA-coated CdTe QDs have small diameter, good stability, high luminescence and long lifetime. Particularly, it was confirmed, using fluorescence correlation spectroscopy (FCS) that, compared with other ligand, MUA formed a thicker ligand layer on the QD surfaces, which will help their stability and conjugation with biomolecules. Furthermore, MUA-coated QDs were successfully used for HeLa cell imaging.

Duman, F. D., et al. (2019). "Bypassing pro-survival and resistance mechanisms of autophagy in EGFR-positive lung cancer cells by targeted delivery of 5FU using theranostic Ag2S quantum dots." J Mater Chem B **7**(46): 7363-7376.

Targeted drug delivery systems that combine imaging and therapeutic functions in a single structure have become very popular in nanomedicine. Near-infrared (NIR) emitting Ag2S quantum dots (QDs) are excellent candidates for this task. Here, we have developed PEGylated Ag2S QDs functionalized with Cetuximab (Cet) antibody and loaded with an anticancer drug, 5-fluorouracil (5FU). These theranostic QDs were used for targeted NIR imaging and treatment of lung cancer using low (H1299) and high (A549) Epidermal Growth Factor Receptor (EGFR) overexpressing cell lines. The Cet conjugated QDs effectively and selectively delivered 5FU to A549 cells and provided significantly enhanced cell death associated with apoptosis. Interestingly, while treatment of cells with free 5FU activated autophagy, a cellular mechanism conferring resistance to cell death, these EGFR targeting multimodal QDs significantly overcame drug resistance compared to 5FU treatment alone. The improved therapeutic outcome of 5FU delivered to A549 cells by Cet conjugated Ag2S QDs is suggested as the synergistic outcome of enhanced receptor mediated uptake of nanoparticles, and hence the drug, coupled with suppressed autophagy even in the absence of addition of an autophagy suppressor.

Durgadas, C. V., et al. (2011). "Fluorescent and superparamagnetic hybrid quantum clusters for magnetic separation and imaging of cancer cells from blood." Nanoscale **3**(11): 4780-4787.

We demonstrate here the generation of fluorescent superparamagnetic quantum clusters through a greener aqueous route by fusing highly fluorescent gold clusters with superparamagnetic nanoparticles. We conjugated transferrin onto the hybrid clusters to get cell accessibility and assessed their hemocompatibility and cytotoxicity. The ability of the clusters to selectively remove cancer cell lines (C6 glioma cells) from fluids including blood and the fluorescent imaging of the separated cells is demonstrated. The pattering of the clusters in response to an external magnetic field is also shown. Efficient cancer cell separation, imaging and magnetic pattering can be realized by the highly hemocompatible and noncytotoxic hybrid clusters reported here. It seems the probe has potential for further exploration in multimodal imaging of circulating cancer cells.

Dutta, K., et al. (2021). "Development of an Efficient Immunosensing Platform by Exploring Single-Walled Carbon Nanohorns (SWCNHs) and Nitrogen Doped Graphene Quantum Dot (N-GQD) Nanocomposite for Early Detection of Cancer Biomarker." ACS Biomater Sci Eng **7**(12): 5541-5554.

In this work, a novel electrochemical immunosensor based on nitrogen doped graphene quantum dot (N-GQD) and single-walled carbon nanohorns (SWCNHs) was developed for the detection of alpha-fetoprotein (AFP), a cancer biomarker. Thus, to fabricate the platform of the immunosensor, nanocomposite architecture was developed by decorating N-GQD on the surface of the SWCNHs. The resulting hybrid architecture (N-GQD@SWCNHs) functioned as an exceptional base for the immobilization of antibody (Anti-AFP) through carbodiimide reaction with good stability and bioactivity. The immunosensor was prepared by evenly distributing the bioconjugates (N-GQD@SWCNHs/Anti-AFP) dispersion on the surface of the glassy carbon electrode, and subsequently blocking the remaining active sites by bovine serum albumin to prevent the nonspecific adsorption. Cyclic

voltammetry and electrochemical impedance spectroscopy technique was employed to investigate the assembly process of the immunosensor. Under optimal conditions, the immunosensor exhibited a broad dynamic range in between 0.001 ng/mL to 200 ng/mL and a low detection limit of 0.25 pg/mL. Furthermore, the sensor showed high selectivity, desirable stability, and reproducibility. Measurements of AFP in human serum gave outstanding recovery within 99.2% and 102.1%. Thus, this investigation and the amplification strategy exhibited a potential role of the developed nanocomposite based sensor for early clinical screening of cancer biomarkers.

Duzagac, F., et al. (2021). "Microfluidic Organoids-on-a-Chip: Quantum Leap in Cancer Research." Cancers (Basel) **13**(4).

Organ-like cell clusters, so-called organoids, which exhibit self-organized and similar organ functionality as the tissue of origin, have provided a whole new level of bioinspiration for ex vivo systems. Microfluidic organoid or organs-on-a-chip platforms are a new group of micro-engineered promising models that recapitulate 3D tissue structure and physiology and combines several advantages of current in vivo and in vitro models. Microfluidics technology is used in numerous applications since it allows us to control and manipulate fluid flows with a high degree of accuracy. This system is an emerging tool for understanding disease development and progression, especially for personalized therapeutic strategies for cancer treatment, which provide well-grounded, cost-effective, powerful, fast, and reproducible results. In this review, we highlight how the organoid-on-a-chip models have improved the potential of efficiency and reproducibility of organoid cultures. More widely, we discuss current challenges and development on organoid culture systems together with microfluidic approaches and their limitations. Finally, we describe the recent progress and potential utilization in the organs-on-a-chip practice.

E, A., et al. (2022). "Structural, vibrational, quantum chemical and thermal investigation of a nutraceutical drug in new zwitterionic cocrystal form (nicotinic acid: catechol) with enhanced cytotoxic activity in cervical cancer HeLa cell line." J Biomol Struct Dyn **40**(13): 5903-5916.

Nicotinic acid is an aphrodisiac, co-crystalized with catechol [NICCAT] in Zwitterionic structure used as unorthodox drugs. The present study, investigates its molecular structure, using X-ray diffraction and q chemical optimization technique. An examination of single-crystal XRD reported that crystal packing was highly stabilized with N.H...O and O-H...O. Hydrogen bond synthons. Besides, a weak C-H...O affinity was also contributed to the powerful molecular construction in crystal packing. To geometrically optimize the molecular structure, we employed the Density Functional Theory (DFT), by adopting the B3LYP function and Hartree-Fock (HF) level, with 6-311++G (d, p) a basic set. Moreover, spectral analyses were detected within an excitation range of 4000-400 cm(-1) using FT.IR and FT-Raman spectroscopy. A comprehensive analysis was executed by comparing optimized molecular geometries and computed excitation spectra with their respective experimental model counterparts. NICCAT thermodynamic functions were detected in the range of 100-1000 K. The thermal strong stability of developed crystals was evaluated by TGA/DTA measured. Powerful biological actions on humans cervical cancer cell line was observed and proved to be effective. The in vitro and in silico anticancer studies show that NICCAT has better activity against human cervical cancer cell line (HeLa) and in bioinformatics analysis.

Elakkiya, V., et al. (2017). "Optical detection of CA 15.3 breast cancer antigen using CdS quantum dot." IET Nanobiotechnol **11**(3): 268-276.

The present study focus on optical sensing of breast cancer antigen 15.3 (CA 15.3) using cadmium sulphide quantum dot (CdS-QD) in saline and serum samples spiked with antigen. The surface of CdS-QD was modified by cysteamine capping followed by tagging of CA 15.3 antibody. The samples were characterised using UV-visible absorption spectroscopy (UV-VIS Spectroscopy), Fourier transform infrared spectroscopy (FTIR), high-resolution transmission electron microscopy (HRTEM) attached with energy-dispersive X-ray spectroscopy, phase contrast inverted epi-fluorescence microscopy and photoluminescence (PL) spectrophotometry (EDS). The CdS-QD showed a mean diameter of 3.02 +/- 0.6 nm. The complex formed after antigen-antibody interaction resulted in distinguishable optical and fluorescence intensity with respect to varying concentration of antigen. The PL study revealed that CA 15.3 antibody labelled CdS QD can detect CA 15.3 tumour marker even at very low concentration of 0.002 KU/L with a constant response time of 15 min. This study clearly indicates that detection of CA 15.3 at low concentration is possible using surface modified CdS QD in serum samples and can find immense applications in biosensor development for detection of breast cancer marker similar to various automated detection kits available in market.

Erogbogbo, F., et al. (2011). "Bioconjugation of luminescent silicon quantum dots for selective uptake by cancer cells." Bioconjug Chem **22**(6): 1081-1088.

Conventional quantum dots have great potential in cancer-related imaging and diagnostic

applications; however, these applications are limited by concerns about the inherent toxicity of their core materials (e.g., cadmium, lead). Virtually all imaging applications require conjugation of the imaging agent to a biologically active molecule to achieve selective uptake or binding. Here, we report a study of biocompatible silicon quantum dots covalently attached to biomolecules including lysine, folate, antimesothelin, and transferrin. The particles possess desirable physical properties, surface chemistry, and optical properties. Folate- and antimesothelin-conjugated silicon quantum dots show selective uptake into Panc-1 cells. This study contributes to the preclinical evaluation of silicon quantum dots and further demonstrates their potential as an imaging agent for cancer applications.

Erogbogbo, F., et al. (2008). "Biocompatible luminescent silicon quantum dots for imaging of cancer cells." ACS Nano **2**(5): 873-878.

Luminescent silicon quantum dots (Si QDs) have great potential for use in biological imaging and diagnostic applications. To exploit this potential, they must remain luminescent and stably dispersed in water and biological fluids over a wide range of pH and salt concentration. There have been many challenges in creating such stable water-dispersible Si QDs, including instability of photoluminescence due their fast oxidation in aqueous environments and the difficulty of attaching hydrophilic molecules to Si QD surfaces. In this paper, we report the preparation of highly stable aqueous suspensions of Si QDs using phospholipid micelles, in which the optical properties of Si nanocrystals are retained. These luminescent micelle-encapsulated Si QDs were used as luminescent labels for pancreatic cancer cells. This paves the way for silicon quantum dots to be a valuable optical probe in biomedical diagnostics.

Esgandari, K., et al. (2021). "Combined treatment with silver graphene quantum dot, radiation, and 17-AAG induces anticancer effects in breast cancer cells." J Cell Physiol **236**(4): 2817-2828.

We aimed to investigate the possible anticancer effects of radiation in combination with 17-allylamino-17-demethoxy geldanamycin (17-AAG) and silver graphene quantum dot (SQD) in breast cancer (BC) cells. MCF-7 BC cells treated with, or without, different concentrations of 17-AAG and synthesized SQD and cellular viability detected. The growth inhibitory effects of low concentrations of 17-AAG with minimally toxic concentration of SQD in combination with 2 Gy of X-ray radiation were examined. The apoptosis induction assessed by acridine orange/ethedium bromide staining. Likewise, the levels of lactate, hydrogen peroxide (H2 O2), nitric oxide (NO) were evaluated. The relative gene expression levels of Bax and Bcl-2 were detected by real-time polymerase chain reaction and the Bax/Bcl-2 expression ratio was determined. Moreover, the protein expression of epidermal growth factor receptor (EGFR) was assessed by western blot analysis. Treatment with low concentrations of 17-AAG and SQD at a minimally toxic concentration promoted inhibition of BC cell growth and induced apoptosis. In addition, significant reduction in cell viability was seen in triple combination versus all double and single treatments. Indeed 17-AAG and SQD in combined with radiation significantly increased the H2 O2 and NO versus single and double treated cases. In addition, triple combination treatment showed decreased lactate level in compared tomonotherapies. EGFR protein expression levels were found to decreased in all double and triple combined cases versus single treatments. Additionally, in double and triple treatments, Bax/Bcl2 ratio were higher in compared to single treatments. Treatment with low concentrations of 17-AAG and SQD at a minimally toxic concentration tends to induce anticancer effects and increase the radiation effects when applied with 2 Gy of radiation versus radiation monotherapy.

Fakhri, A., et al. (2017). "Preparation and characterization of Fe3O4-Ag2O quantum dots decorated cellulose nanofibers as a carrier of anticancer drugs for skin cancer." J Photochem Photobiol B **175**: 83-88.

The Best performance drug delivery systems designed with Fe3O4-Ag2O quantum dots decorated cellulose nanofibers which that grafted with Etoposide and Methotrexate. Morphology properties were characterized by Scanning and Transmittance electron microscopy. The crystalline structure of prepared sample was evaluated using by X-ray diffraction. The vibrating sample magnetometer analysis was used for magnetic behavior of samples. The size distributions of Fe3O4-Ag2O QDs/Cellulose fibers nanocomposites indicate that the average diameter was 62.5nm. The Saturation magnetization (Ms) indicates the Fe3O4-Ag2O QDs/Cellulose fibers nanocomposites have ferromagnetic properties in nature. For make carrier, the Iron and Silver should be binds to cellulose nanofibers and to drug molecules and observe in UV-vis spectroscopy. The drug release kinetics was studied in vitro as spectrophotometrically. The release of Etoposide and Methotrexate were carried out with a constant speed, and the equilibrium reached at 24 and 30h with a total amount 78.94% and 63.84%, respectively. The results demonstrated that the obtained Fe3O4-Ag2O quantum dots/cellulose fibers nanocomposites could be applied for drug delivery systems. Cytotoxicity and antioxidant study confirmed the activity of the drug incorporated in nanocomposites. In addition, the cytotoxicity of drug was increased when loaded on nanocomposites, compared to pure Fe3O4-Ag2O quantum dots/cellulose fibers nanocomposites.

Fakhroueian, Z., et al. (2022). "Anticancer properties of novel zinc oxide quantum dot nanoparticles against breast cancer stem-like cells." Anticancer Drugs **33**(1): e311-e326.

Cancer stem cells (CSCs) play an essential role in cancer development, metastasis, relapse, and resistance to treatment. In this article, the effects of three synthesized ZnO nanofluids on proliferation, apoptosis, and stemness markers of breast cancer stem-like cells are reported. The antiproliferative and apoptotic properties of ZnO nanoparticles were evaluated on breast cancer stem-like cell-enriched mammospheres by MTS assay and flowcytometry, respectively. The expression of stemness markers, including WNT1, NOTCH1, beta-catenin, CXCR4, SOX2, and ALDH3A1 was assessed by real-time PCR. Western blotting was used to analyze the phosphorylation of Janus kinase 2 (JAK2) and Signal Transducer and Activator of Transcription 3 (STAT3). Markers of stemness were significantly decreased by ZnO nanofluids, especially sample (c) with code ZnO-148 with a different order of addition of polyethylene glycol solution at the end of formulation, which considerably decreased all the markers compared to the controls. All the studied ZnO nanofluids considerably reduced viability and induced apoptosis of spheroidal and parental cells, with ZnO-148 presenting the most effective activity. Using CD95L as a death ligand and ZB4 as an extrinsic apoptotic pathway blocker, it was revealed that none of the nanoparticles induced apoptosis through the extrinsic pathway. Results also showed a marked inhibition of the JAK/STAT pathway by ZnO nanoparticles; confirmed by downregulation of Mcl-1 and Bcl-XL expression. The present data demonstrated that ZnO nanofluids could combat breast CSCs via decreasing stemness markers, stimulating apoptosis, and suppressing JAK/STAT activity.

Fan, H. Y., et al. (2019). "Graphene quantum dots (GQDs)-based nanomaterials for improving photodynamic therapy in cancer treatment." Eur J Med Chem **182**: 111620.

Graphene quantum dots (GQDs) as novel nanomaterials, have received significant interest in the field of biomedical applications. It is worth noting that a large amount of research is devoted to GQDs-based nanocomposites for cancer treatment, especially for photodynamic therapy (PDT), in that they can act not only as more favorable photosensitizers (PSs) but also nanoplatforms for delivering PSs. In this review, the biological behavior and physicochemical properties of GQDs for PDT are described in detail, and the application of GQDs-based nanocomposites in improved PDT and PDT-based combination therapies is analyzed, which may provide a new strategy for designing efficient PDT systems for cancer treatment.

Fan, L., et al. (2016). "Identification of serum miRNAs by nano-quantum dots microarray as diagnostic biomarkers for early detection of non-small cell lung cancer." Tumour Biol **37**(6): 7777-7784.

Circulating microRNAs (miRNAs) are potential noninvasive biomarkers for cancer detection. We used preoperative serum samples from non-small cell lung cancer (NSCLC) patients and healthy controls to investigate whether serum levels of candidate miRNAs could be used as diagnostic biomarkers in patients with resectable NSCLC and whether they were associated with clinicopathologic characteristics. We initially detected expression of 12 miRNAs using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) in preoperative serum samples of 94 NSCLC patients and 58 healthy controls. We further validated our results using the fluorescence quantum dots liquid bead array for differentially expressed miRNAs in serum samples of 70 NSCLC patients and 54 healthy controls. Receiver operating characteristic (ROC) analysis was performed to select the best diagnostic miRNA cutoff value. A predictive model of miRNAs for NSCLC was derived by multivariate logistic regression. We found that five serum miRNAs (miR-16-5p, miR-17b-5p, miR-19-3p, miR-20a-5p, and miR-92-3p) were significantly downregulated in NSCLC, while miR-15b-5p was significantly upregulated ($p < 0.05$). Multivariate logistic regression analysis revealed that miR-15b-5p, miR-16-5p, and miR-20a-5p expression were independent diagnostic factors for the identification of patients with NSCLC after adjustment for patient's age and sex. In addition, the expression of serum miR-106-5p was higher in stage I than in stages IIa-IIIb, and no significant association was observed between expression of miRNAs and other variables including pathological type, tumor size, and lymph nodes status. Six serum miRNAs could potentially serve as noninvasive diagnostic biomarkers for resectable NSCLC. The predictive model combining miR-15b-5p, miR-16-5p, and miR-20a-5p was the best diagnostic approach.

Fan, Z., et al. (2017). "pH-Responsive fluorescent graphene quantum dots for fluorescence-guided cancer surgery and diagnosis." Nanoscale **9**(15): 4928-4933.

Cancer remains a major cause of morbidity and mortality around the world. Improved cancer treatment requires enhancement of cancer diagnosis and detection. To achieve this goal, here we report a novel imaging probe, pH-responsive fluorescent graphene quantum dots (pRF-GQDs). pRF-GQDs were prepared by electrolysis of graphite rods in sodium p-toluenesulfonate acetonitrile solution. The resulting

pRF-GQDs, which have minimal toxicity, display a sharp fluorescence transition between green and blue at pH 6.8, a pH matching the acidic extracellular microenvironment in solid tumors. We found that this unique fluorescence switch property allows tumors to be distinguished from normal tissues. In addition to fluorescence, pRF-GQDs also exhibit upconversion photoluminescence (UCPL). We demonstrate that the combination of UCPL and fluorescence switch enables detection of solid tumors of different origin at an early developmental stage. Therefore, pRF-GQDs have great potential to be used as a universal probe for fluorescence-guided cancer surgery and cancer diagnosis.

Fang, M., et al. (2017). "Applications of Quantum Dots in Cancer Detection and Diagnosis: A Review." J Biomed Nanotechnol **13**(1): 1-16.

The mechanisms of carcinogenesis, cancer invasion and metastasis remain unclear because of the complexity of cancer cells and tumor microenvironment. Thus, the urgent development of a novel approach for cancer detection and real-time monitoring is crucial in order to decipher the intricate molecular information responsible for tumor biological behaviors. Quantum dots (QDs) are engineered fluorescent nanoparticles with unique optical and chemical properties, which have shown a great potential as promising platforms for biomedical applications. Here, we focus on the clinical applications of quantum dot-based nanotechnology in cancer detection and diagnosis, covering topics on individual cancer diagnosis and treatment by in-vitro and in-vivo molecular imaging technologies, sentinel lymph node (SLN) mapping, cancer associated proteins detection in blood, circulation tumor cells (CTCs) detection, and in-depth understanding of the biological behaviors from the perspective of tumor microenvironment. In addition, the major challenges in translating quantum dot-based detection methodologies into clinical applications and promising future directions are also discussed.

Fang, M., et al. (2012). "Quantum dots for cancer research: current status, remaining issues, and future perspectives." Cancer Biol Med **9**(3): 151-163.

Cancer is a major threat to public health in the 21st century because it is one of the leading causes of death worldwide. The mechanisms of carcinogenesis, cancer invasion, and metastasis remain unclear. Thus, the development of a novel approach for cancer detection is urgent, and real-time monitoring is crucial in revealing its underlying biological mechanisms. With the optical and chemical advantages of quantum dots (QDs), QD-based nanotechnology is helpful in constructing a biomedical imaging platform for cancer behavior study. This review mainly focuses on the application of QD-based nanotechnology in cancer cell imaging and tumor microenvironment studies both in vivo and in vitro, as well as the remaining issues and future perspectives.

Fang, M., et al. (2013). "Quantum dots-based in situ molecular imaging of dynamic changes of collagen IV during cancer invasion." Biomaterials **34**(34): 8708-8717.

Cancer invasion and metastasis remains the root cause of mortality. This process involves alterations of tumor microenvironment, particularly the remodeling of extracellular matrix, characterized by collagen IV uncoiling, degradation, fragments deposition and cross-linking. Quantum dots-labeled molecular probes are promising platforms to simultaneously study several subtle changes of key biomolecules, because of their unique optical and chemical properties. Here we report on a quantum dots-based imaging technology to study key components in tumor microenvironment during cancer progression, so as to gain new insights into the role of collagen IV plays, to define the cancer "invasion unit" and to develop the "pulse-mode" of cancer invasion.

Fang, Y., et al. (2022). "Artificial Assembled Macrophage Co-Deliver Black Phosphorus Quantum Dot and CDK4/6 Inhibitor for Colorectal Cancer Triple-Therapy." ACS Appl Mater Interfaces **14**(18): 20628-20640.

In recent years, therapeutic strategies based on macrophages have been inspiringly developed, but due to the high intricacy and immunosuppression of the tumor microenvironment, the widespread use of these strategies still faces significant challenges. Herein, an artificial assembled macrophage concept (AB@LM) was presented to imitate the main antitumor abilities of macrophages of tumor targeting, promoting the antitumor immunity, and direct tumor-killing effects. The artificial assembled macrophage (AB@LM) was prepared through an extrusion method, which is to fuse the macrophage membrane with abemaciclib and black phosphorus quantum dot (BPQD)-loaded liposomes. AB@LM showed good stability and tumor targeting ability with the help of macrophage membrane. Furthermore, AB@LM reversed the immunosuppressive tumor microenvironment by inhibiting regulatory T cells (Tregs) and stimulating the maturation of antigen-presenting cells to activate the antitumor immune response through triggering an immunogenic cell death effect. More importantly, in the colorectal tumor model in vivo, a strong cooperative therapeutic effect of photo/chemo/immunotherapy was observed with high tumor inhibition rate (95.3 +/- 2.05%). In conclusion, AB@LM exhibits excellent antitumor efficacy by intelligently mimicking the

abilities of macrophages. A promising therapeutic strategy for tumor treatment based on imitating macrophages was provided in this study.

Farias, P. M., et al. (2009). "Semiconductor fluorescent quantum dots: efficient biolabels in cancer diagnostics." Methods Mol Biol **544**: 407-419.

We present and discuss results and features related to the synthesis of water-soluble semiconductor quantum dots and their application as fluorescent biomarkers in cancer diagnostics. We have prepared and applied different core-shell quantum dots, such as cadmium telluride-cadmium sulfide, CdTe-CdS, and cadmium sulfide-cadmium hydroxide, CdS/Cd(OH)(2), in living healthy and neoplastic cells and tissues samples. The CdS/Cd(OH)(2) quantum dots presented the best results, maintaining high levels of luminescence as well as high photostability in cells and tissues. Labeled tissues and cells were analyzed by their resulting fluorescence, via conventional fluorescence microscopy or via laser scanning confocal microscopy. The procedure presented in this work was shown to be efficient as a potential tool for fast and precise cancer diagnostics.

Fatehi, D., et al. (2014). "In vivo imaging of brain cancer using epidermal growth factor single domain antibody bioconjugated to near-infrared quantum dots." J Nanosci Nanotechnol **14**(7): 5355-5362.

Diagnosis of glioblastoma multiform (GBM) with MRI lacks molecular information and requires a biopsy for pathologic confirmation. The EGFRvIII, is a constitutively active mutant of the EGF receptor, identified in a high percentage of brain cancers and associated with increased invasiveness and resistance, making it a good target to improve imaging and diagnosis. The present study shows that conjugation of near-infrared quantum dot (Qd800) to an anti-EGFRvIII single domain antibody, made of the variable region with an extra cysteine for site-specific conjugation (EG2-Cys), increased its internalization in U87MG-EGFRvIII cells in vitro compared to Qd800 conjugated with the Fc region of the antibody (EG2-hFc) or unconjugated. EG2-Cys also improved the contrast in Near-Infrared Imaging of mice bearing orthotopic glioblastoma. The increased accumulation was confirmed by fluorescence microscopy of brain sections. The specificity of EG2-Cys in brain tumor expressing the EGFRvIII mutant receptor may provide an accurate less invasive diagnosis and determine the level of tumor aggressiveness and resistance.

Fatima, B., et al. (2020). "Catalase immobilized antimonene quantum dots used as an electrochemical biosensor for quantitative determination of H2O2 from CA-125 diagnosed ovarian cancer samples." Mater Sci Eng C Mater Biol Appl **117**: 111296.

A selective and cost-effective biosensor based on catalase immobilized antimonene quantum dots modified glassy carbon electrode (Cat@AMQDs-GCE) is designed for the first time to determine hydrogen peroxide (H2O2). Antimonene quantum dots (AMQDs) are synthesized by a single step method, characterized by various analytical techniques and applied to the electrochemical sensing of hydrogen peroxide. Catalase enzyme specific for H2O2 reduction is immobilized onto AMQDs to facilitate its detection by cyclic voltammetry and amperometry. Concentration, scan rate, pH, stability and selectivity are optimized. Linearity of Cat@AMQDs-GCE is determined as 0.989 with limit of detection as 4.4muM. Amperometric measurements show recovery of 95 to 103.4% for H2O2 from human serum samples. Cat@AMQDs-GCE is electrochemically stable up to 30cycles, reducing the cost of analysis. Cat@AMQDs-GCE shows good selectivity in presence of ascorbic acid, dopamine, leucine and glucose. Prepared electrode is also applied for the quantitative determination of H2O2 from ovarian cancer serum. CA 125 concentration is previously determined by Elecsys CA 125 II Assay. Results demonstrate that concentration of H2O2 increases with increasing levels of CA125 in serum.

Fatima, I., et al. (2021). "Quantum Dots: Synthesis, Antibody Conjugation, and HER2-Receptor Targeting for Breast Cancer Therapy." J Funct Biomater **12**(4).

Breast cancer is becoming one of the main lethal carcinomas in the recent era, and its occurrence rate is increasing day by day. There are different breast cancer biomarkers, and their overexpression takes place in the metastasis of cancer cells. The most prevalent breast cancer biomarker is the human epidermal growth factor receptor2 (HER2). As this biomarker is overexpressed in malignant breast tissues, it has become the main focus in targeted therapies to fight breast cancer. There is a cascade of mechanisms involved in metastasis and cell proliferation in cancer cells. Nanotechnology has become extremely advanced in targeting and imaging cancerous cells. Quantum dots (QDs) are semiconductor NPs, and they are used for bioimaging, biolabeling, and biosensing. They are synthesized by different approaches such as top-down, bottom-up, and synthetic methods. Fully human monoclonal antibodies synthesized using transgenic mice having human immunoglobulin are used to target malignant cells. For the HER2 receptor, herceptin((R)) (trastuzumab) is the most specific antibody (Ab), and it is conjugated with QDs by using different types of coupling mechanisms. This quantum dot monoclonal antibody (QD-mAb) conjugate is localized by injecting it into the blood vessel. After the injection, it goes

through a series of steps to reach the intracellular space, and bioimaging of specifically the HER2 receptor occurs, where apoptosis of the cancer cells takes place either by the liberation of Ab or the free radicals.

Foda, M. F., et al. (2014). "Biocompatible and highly luminescent near-infrared CuInS(2)/ZnS quantum dots embedded silica beads for cancer cell imaging." ACS Appl Mater Interfaces **6**(3): 2011-2017.

Bright and stable CuInS2/ZnS@SiO2 nanoparticles with near-infrared (NIR) emission were competently prepared by incorporating the as-prepared hydrophobic CuInS2/ZnS quantum dots (QDs) directly into lipophilic silane micelles and subsequently an exterior silica shell was formed. The obtained CuInS2/ZnS@SiO2 nanoparticles homogeneously comprised both single-core and multicore remarkable CuInS2/ZnS QDs, while the silica shell thickness could be controlled to within 5-10 nm and their overall size was 17-25 nm. Also, the functionalized CuInS2/ZnS QDs encapsulated in the silica spheres, expedited their bioconjugation with holo-Transferrin (Tf) for further cancer cell imaging. The CuInS2/ZnS@SiO2 nanoparticles not only showed a dominant NIR band-edge luminescence at 650-720 nm with a quantum yield (QY) between 30 and 50%, without a recognized photoluminescence (PL) red shift, but also exhibited excellent PL and colloidal stability in aqueous media. Impressively, the cytotoxicity studies revealed minor suppression on cell viability under both CuInS2/ZnS@SiO2 and CuInS2/ZnS@SiO2@Tf concentrations up to 1 mg/mL. The application in live-cell imaging revealed that the potential of CuInS2/ZnS QDs as biocompatible, robust, cadmium-free, and brilliant NIR emitters is considered promising for fluorescent labels.

Forder, J., et al. (2019). "A Physiologically-Based Pharmacokinetic Model for Targeting Calcitriol-Conjugated Quantum Dots to Inflammatory Breast Cancer Cells." Clin Transl Sci **12**(6): 617-624.

Quantum dots (QDs) conjugated with 1,25 dihydroxyvitamin D3 (calcitriol) and Mucin-1 (MUC-1) antibodies (SM3) have been found to target inflammatory breast cancer (IBC) tumors and reduce proliferation, migration, and differentiation of these tumors in mice. A physiologically-based pharmacokinetic model has been constructed and optimized to match experimental data for multiple QDs: control QDs, QDs conjugated with calcitriol, and QDs conjugated with both calcitriol and SM3 MUC1 antibodies. The model predicts continuous QD concentration for key tissues in mice distinguished by IBC stage (healthy, early-stage, and late-stage). Experimental and clinical efforts in QD treatment of IBC can be augmented by in silico simulations that predict the short-term and long-term behavior of QD treatment regimens.

Freitas, M., et al. (2020). "Quantum dots as nanolabels for breast cancer biomarker HER2-ECD analysis in human serum." Talanta **208**: 120430.

Early detection of cancer increases the possibility for an adequate and successful treatment of the disease. Therefore, in this work, a disposable electrochemical immunosensor for the front-line detection of the ExtraCellular Domain of the Human Epidermal growth factor Receptor 2 (HER2-ECD), a breast cancer biomarker, in a simple and efficient manner is presented. Bare screen-printed carbon electrodes were selected as the transducer onto which a sandwich immunoassay was developed. The affinity process was detected through the use of an electroactive label, core/shell CdSe@ZnS Quantum Dots, by differential pulse anodic stripping voltammetry in a total time assay of 2h, with an actual hands-on time of less than 30min. The proposed immunosensor responded linearly to HER2-ECD concentration within a wide range (10-150ng/mL), showing acceptable precision and a limit of detection (2.1ng/mL, corresponding to a detected amount (sample volume=40muL) of 1.18fmol) which is about 7 times lower than the established cut-off value (15ng/mL). The usefulness of the developed methodology was tested through the analysis of spiked human serum samples. The reliability of the presented biosensor for the selective screening of HER2-ECD was confirmed by analysing another breast cancer biomarker (CA15-3) and several human serum proteins.

Freitas, M., et al. (2020). "Immunomagnetic bead-based bioassay for the voltammetric analysis of the breast cancer biomarker HER2-ECD and tumour cells using quantum dots as detection labels." Mikrochim Acta **187**(3): 184.

An electrochemical magnetic immunosensing strategy was developed for the determination of HER2-ECD, a breast cancer biomarker, and breast cancer cells in human serum. A sandwich assay was performed on carboxylic acid-functionalized magnetic beads (MBs) using a screen-printed carbon electrode (SPCE) as transducer surface. The affinity process was detected using electroactive labels; core/shell streptavidin-modified CdSe@ZnS Quantum Dots (QDs). Cd(2+) ions, released from the QDs, were determined by differential pulse anodic stripping voltammetry (DPASV). An assay time of 90 min, with an actual hands-on time of about 20 min, a linear range between 0.50-50 ng.mL(-1) of HER2-ECD and a limit of detection of 0.29 ng.mL(-1) were achieved. Analysis of live breast cancer cells was also performed using the optimized assay. Breast cancer cell lines SK-BR-3 (a HER2-positive cell line), MDA-MB-231 (a HER2-

negative cell line) and MCF-7 (a cell line with low HER2 expression) were tested. The selectivity of the assay towards SK-BR-3 cells was confirmed. A concentration-dependent signal that was 12.5x higher than the signal obtained for the HER2-negative cells (MDA-MB-231) and a limit of detection of 2 cells.mL(-1) was obtained. Graphical abstractSchematic representation of the electrochemical immunomagnetic assay for the determination of the breast cancer biomarker HER2-ECD and cancer cells using magnetic beads (MBs), a screen-printed carbon electrode (SPCE) as transducer surface and quantum dots (QD) as electroactive labels.

Frieler, M., et al. (2021). "Effects of Doxorubicin Delivery by Nitrogen-Doped Graphene Quantum Dots on Cancer Cell Growth: Experimental Study and Mathematical Modeling." Nanomaterials (Basel) **11**(1).

With 18 million new cases diagnosed each year worldwide, cancer strongly impacts both science and society. Current models of cancer cell growth and therapeutic efficacy in vitro are time-dependent and often do not consider the Emax value (the maximum reduction in the growth rate), leading to inconsistencies in the obtained IC50 (concentration of the drug at half maximum effect). In this work, we introduce a new dual experimental/modeling approach to model HeLa and MCF-7 cancer cell growth and assess the efficacy of doxorubicin chemotherapeutics, whether alone or delivered by novel nitrogen-doped graphene quantum dots (N-GQDs). These biocompatible/biodegradable nanoparticles were used for the first time in this work for the delivery and fluorescence tracking of doxorubicin, ultimately decreasing its IC50 by over 1.5 and allowing for the use of up to 10 times lower doses of the drug to achieve the same therapeutic effect. Based on the experimental in vitro studies with nanomaterial-delivered chemotherapy, we also developed a method of cancer cell growth modeling that (1) includes an Emax value, which is often not characterized, and (2), most importantly, is measurement time-independent. This will allow for the more consistent assessment of the efficiency of anti-cancer drugs and nanomaterial-delivered formulations, as well as efficacy improvements of nanomaterial delivery.

Fujii, Y. R. (2018). "Quantum Language of MicroRNA: Application for New Cancer Therapeutic Targets." Methods Mol Biol **1733**: 145-157.

MicroRNA (miRNA) is the noncoding gene: therefore, the miRNA gene inheritably controls protein gene expression through transcriptional and post-transcriptional levels. Aberrant expression of miRNA genes causes various human diseases, especially cancers. Although cancer is a complex disease, cancer/miRNA implication has yet been grasped from the perspective of miRNA profile in bed side. Since miRNA is the mobile genetic element, the clinical verification of miRNA in microvesicle of blood is too much straggle to predict potential cancer/miRNA associations without bioinformatical computing. Further, experimental investigation of miRNA/cancer pathways is expensive and time-consuming. While the accumulated data (big data) of miRNA profiles has been on line as the databases in cancers, using the database algorithms for miRNA target prediction have reduced required time for conventional experiments and have cut the cost. Computational prediction of miRNA/target mRNA has shown numerous significant outcomes that are unobtainable only by experimental approaches. However, ID of miRNA in the annotation is an arbitrary number and the ID is not related with miRNA its functions. Therefore, it has not been physicochemically shown why multiple miRNAs in blood or tissues are useful for diagnosis and porgnosis of human diseases or why function of single miRNA in cancer is rendered to oncomir or tumopr suppressor. In addition, it is less cleared why environmental factors, such as temperature, radiation, therapeutic anti-cancer immune or chemical agents can alter the expression of miRNAs in the cell. The ceRNA theory would not be enough for the investigation of such subjects. Given miRNA/target prediction tools, to elucidate such issues with computer simulation we have previously introduced the quantum miRNA/miRNA interaction as a new scoring using big database. The quantum score was implicated in miRNA synergisms in cancer and participated in the miRNA/target interaction on human diseases. On the other hand, ribosomal RNA (rRNA) is the dominant RNA species of the cells. It is well known that ribosomopathies, such as Diamond-Blackfan anemia, dyskeratiosis congenital, Shwachman-Diamond syndrome, 5q-myelodysplastic syndrome, Treacher Collins syndrome, cartilage-hair hypoplasia, North American Indian childhood cirrhosis, isolated congenital asplenia, Bowen-Conradi syndrome and cancer are caused by altered expression of ribosomal proteins or rRNA genes. We have proposed the hypothesis that the interaction among miRNAs from rRNA and/or other cellular miRNAs would be involved into cancer as the ribosomopathy. Subsequently, we found rRNA-derived miRNAs (rmiRNAs) by using the sequence homology search (miPS) with miRNA database (miRBase). Further, the pathway related with cancer between rmiRNA/target protein gene was predicted by miRNA entangling target sorting (METS) algorithm. In this chapter, we describe about the usage of in silico miRNA identification program, miRNA/target prediction search through the database and quantum language of miRNA by the METS, and the ontology analysis. In particular, the METS algorithm according to the quantum value would be useful

simulator to discover a new therapeutic target aganist cancer. It may also partly contribute to the elucidation of complex mechanisms and development of agents of anti-cancer.

Ganesan, S., et al. (2020). "Wrinkled metal based quantum sensor for In vitro cancer diagnosis." Biosens Bioelectron **151**: 111967.

This article presents a unique 3D biocompatible Aluminum-based quantum structure (QS) for in vitro cancer detection using Surface Enhanced Raman Scattering (SERS). The Al-based QSs fabricated using ultrashort pulsed laser are of two distinct surface characters, wrinkled and smooth spherical. The limit of detection for chemical sensing of Crystal Violet and Rhodamine 6G by the Al-QS was driven up to single molecule sensing (femtomolar concentration). Biological sensing of cysteine, a disease biomarker and carcinoembryonic antigen (CEA), a cancer biomarker was also tested by the Al-QS. The ability of in vitro cell detection using Al-QS was analyzed with three cell lines, mammalian fibroblast and pancreatic and lung cancer cells. The Al-QS were up taken by the cells through label-free self-internalization and were sensed by SERS. Further assay was performed to differentiate cancerous and non-cancerous cells by measuring lipid and protein peak intensity within the cells. The result of this research indicated that SERS based Al-QS could be a suitable candidate for the early diagnosis of cancer.

Gao, J., et al. (2016). "Direct Synthesis of Water-Soluble Aptamer-Ag2 S Quantum Dots at Ambient Temperature for Specific Imaging and Photothermal Therapy of Cancer." Adv Healthc Mater **5**(18): 2437-2449.

Water-soluble Ag2 S near-infrared (NIR) fluorescent quantum dots (QDs) are directly synthesized at ambient temperature for specific cancer imaging and photothermal therapy (PTT) using a designed aptamer (Apt43) as template, which consists of the following two fragments: an aptamer S2.2 sequence for specifically recognizing the cancer cells and an 18-cytosine (18-C) extending spacer for growing Ag2 S QDs. The synthesized Ag2 S QDs (Apt43-Ag2 S QDs), which exhibit strong absorption and fluorescence emission in the NIR region and high photothermal conversion capabilities, can specifically recognize MCF-7 cells (human breast cancer cells) and are usable as a highly intensified imaging agent for cancer diagnosis. Moreover, they can be applied as photothermal agents for the in vitro killing of MCF-7 cells and the in vivo ablation of tumors, which were constructed on the bodies of nude mice. MCF-7 cells almost quantitatively die after they are incubated with the QDs (at 100 mug mL(-1)) for 2 h and irradiated under an 808 nm laser at a power density of 1.0 W cm(-2) for 10 min. The tumors on the nude mice can also be effectively ablated without regrowth during the period of observation (at least 20 d) after PTT.

Gao, X., et al. (2004). "In vivo cancer targeting and imaging with semiconductor quantum dots." Nat Biotechnol **22**(8): 969-976.

We describe the development of multifunctional nanoparticle probes based on semiconductor quantum dots (QDs) for cancer targeting and imaging in living animals. The structural design involves encapsulating luminescent QDs with an ABC triblock copolymer and linking this amphiphilic polymer to tumor-targeting ligands and drug-delivery functionalities. In vivo targeting studies of human prostate cancer growing in nude mice indicate that the QD probes accumulate at tumors both by the enhanced permeability and retention of tumor sites and by antibody binding to cancer-specific cell surface biomarkers. Using both subcutaneous injection of QD-tagged cancer cells and systemic injection of multifunctional QD probes, we have achieved sensitive and multicolor fluorescence imaging of cancer cells under in vivo conditions. We have also integrated a whole-body macro-illumination system with wavelength-resolved spectral imaging for efficient background removal and precise delineation of weak spectral signatures. These results raise new possibilities for ultrasensitive and multiplexed imaging of molecular targets in vivo.

Gao, X. and S. R. Dave (2007). "Quantum dots for cancer molecular imaging." Adv Exp Med Biol **620**: 57-73.

Quantum dots (QDs), tiny light-emitting particles on the nanometer scale, are emerging as a new class of fluorescent probes for biomolecular and cellular imaging. In comparison with organic dyes and fluorescent proteins, quantum dots have unique optical and electronic properties such as size-tunable light emission, improved signal brightness, resistance against photobleaching, and simultaneous excitation of multiple fluorescence colors. These properties are most promising for improving the sensitivity of molecular imaging and quantitative cellular analysis by 1-2 orders of magnitude. Recent advances have led to multifunctional nanoparticle probes that are highly bright and stable under complex in-vivo conditions. A new structural design involves encapsulating luminescent QDs with amphiphilic block copolymers, and linking the polymer coating to tumor-targeting ligands and drug-delivery functionalities. Polymer-encapsulated QDs are essentially nontoxic to cells and small animals, but their long-term in-vivo toxicity and degradation need more careful studies. Nonetheless, bioconjugated QDs have raised new possibilities for

ultrasensitive and multiplexed imaging of molecular targets in living cells and animal models.

Gazouli, M., et al. (2012). "Development of a quantum-dot-labelled magnetic immunoassay method for circulating colorectal cancer cell detection." World J Gastroenterol **18**(32): 4419-4426.

AIM: To detect of colorectal cancer (CRC) circulating tumour cells (CTCs) surface antigens, we present an assay incorporating cadmium selenide quantum dots (QDs) in these paper. METHODS: The principle of the assay is the immunomagnetic separation of CTCs from body fluids in conjunction with QDs, using specific antibody biomarkers: epithelial cell adhesion molecule antibody, and monoclonal cytokeratin 19 antibody. The detection signal was acquired from the fluorescence signal of QDs. For the evaluation of the performance, the method under study was used to isolate the human colon adenocarcinoma cell line (DLD-1) and CTCs from CRC patients' peripheral blood. RESULTS: The minimum detection limit of the assay was defined to 10 DLD-1 CRC cells/mL as fluorescence was measured with a spectrofluorometer. Fluorescence-activated cell sorting analysis and Real Time RT-PCR, they both have also been used to evaluate the performance of the described method. In conclusion, we developed a simple, sensitive, efficient and of lower cost (than the existing ones) method for the detection of CRC CTCs in human samples. We have accomplished these results by using magnetic bead isolation and subsequent QD fluorescence detection. CONCLUSION: The method described here can be easily adjusted for any other protein target of either the CTC or the host.

Geng, X. F., et al. (2016). "Quantum dot-based molecular imaging of cancer cell growth using a clone formation assay." Mol Med Rep **14**(4): 3007-3012.

This aim of the present study was to investigate clonal growth behavior and analyze the proliferation characteristics of cancer cells. The MCF7 human breast cancer cell line, SW480 human colon cancer cell line and SGC7901 human gastric cancer cell line were selected to investigate the morphology of cell clones. Quantum dotbased molecular targeted imaging techniques (which stained pancytokeratin in the cytoplasm green and Ki67 in the cell nucleus yellow or red) were used to investigate the clone formation rate, cell morphology, discrete tendency, and Ki67 expression and distribution in clones. From the cell clone formation assay, the MCF7, SW480 and SGC7901 cells were observed to form clones on days 6, 8 and 12 of cell culture, respectively. These three types of cells had heterogeneous morphology, large nuclear:cytoplasmic ratios, and conspicuous pathological mitotic features. The cells at the clone periphery formed multiple pseudopodium. In certain clones, cancer cells at the borderline were separated from the central cell clusters or presented a discrete tendency. With quantum dotbased molecular targeted imaging techniques, cells with strong Ki67 expression were predominantly shown to be distributed at the clone periphery, or concentrated on one side of the clones. In conclusion, cancer cell clones showed asymmetric growth behavior, and Ki67 was widely expressed in clones of these three cell lines, with strong expression around the clones, or aggregated at one side. Cell clone formation assay based on quantum dots molecular imaging offered a novel method to study the proliferative features of cancer cells, thus providing a further insight into tumor biology.

Geraci, J. (2021). "Shattering cancer with quantum machine learning: A preview." Patterns (N Y) **2**(6): 100281.

Machine learning has become a standard tool for medical researchers attempting to model disease in various ways, including building models to predict response to medications, classifying disease subtypes, and discovering new therapies. In this preview, we review a paper that utilizes quantum computation in order to tackle a critical issue that exists with medical datasets: they are small, in that they contain few samples. The authors' work demonstrates the possibility that these quantum-based methods may provide an advantage for small datasets and thus have a real impact for medical researchers in the future.

Geraldo, D. A., et al. (2011). "Supramolecular complexes of quantum dots and a polyamidoamine (PAMAM)-folate derivative for molecular imaging of cancer cells." Anal Bioanal Chem **400**(2): 483-492.

Polyamidoamine (PAMAM) dendrimers and water-soluble 3-mercaptopropionic acid (MPA)-capped CdSe quantum dots (QDs) were combined to produce a new gel containing supramolecular complexes of QDs/PAMAM dendrimers. The formation of the QDs/PAMAM supramolecular complexes was confirmed by high resolution electron microscopy and Fourier transform infrared (FTIR) analyses. Molecular dynamics simulations corroborated the structure of the new QDs/PAMAM-based supramolecular compound. Finally, on the basis of the prominent fluorescent properties of the supramolecular complexes, PAMAM dendrimer was functionalized with folic acid to produce a new QDs/PAMAM-folate derivative that showed an efficient and selective performance as a marker for gastric cancer cells.

Gerard, V. A., et al. (2011). "Folic acid modified gelatine coated quantum dots as potential reagents for in vitro cancer diagnostics." J Nanobiotechnology **9**: 50.

BACKGROUND: Gelatine coating was previously shown to effectively reduce the cytotoxicity of CdTe Quantum Dots (QDs) which was a first step towards utilising them for biomedical applications. To be useful they also need to be target-specific which can be achieved by conjugating them with Folic Acid (FA). RESULTS: The modification of QDs with FA via an original "one-pot" synthetic route was proved successful by a range of characterisation techniques including UV-visible absorption spectroscopy, Photoluminescence (PL) emission spectroscopy, fluorescence life-time measurements, Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS). The resulting nanocomposites were tested in Caco-2 cell cultures which over-express FA receptors. The presence of FA on the surface of QDs significantly improved the uptake by targeted cells. CONCLUSIONS: The modification with folic acid enabled to achieve a significant cellular uptake and cytotoxicity towards a selected cancer cell lines (Caco-2) of gelatine-coated TGA-CdTe quantum dots, which demonstrated good potential for in vitro cancer diagnostics.

Geszke, M., et al. (2011). "Folic acid-conjugated core/shell ZnS:Mn/ZnS quantum dots as targeted probes for two photon fluorescence imaging of cancer cells." Acta Biomater **7**(3): 1327-1338.

This work presents a novel approach to producing water soluble manganese-doped core/shell ZnS/ZnS quantum dots (ZnS:Mn/ZnS). The Mn-doped ZnS core was prepared through a nucleation doping strategy and a ZnS shell was grown on ZnS:Mn d-dots by decomposition of Zn(2+)-3-mercaptopropionic acid (MPA) complexes at 100 degrees C. It was found that the Mn2+(4)T1-->6A1 fluorescence emission at approximately 590 nm significantly increased after growth of the shell when the Mn2+ doping content was 4.0 at.%. A photoluminescence quantum yield of approximately 22% was obtained for core/shell nanocrystals. The nanoparticles were structurally and compositionally characterized by transmission electron microscopy, X-ray diffraction, X-ray photoelectron spectroscopy, and dynamic light scattering. The surface MPA molecules favor the dispersion of ZnS:Mn/ZnS QDs in aqueous media and make possible conjugation with targeting folic acid molecules. The folate receptor-mediated delivery of folic acid-conjugated ZnS:Mn/ZnS QDs was demonstrated using confocal microscopy with biphotonic excitation. Bare and folate-conjugated QDs exhibit only weak cytotoxicity towards folate receptor-positive T47D cancer cells and MCF-7 cells, used as a reference, at high concentrations (mmolar range) after 72h incubation.

Ghanbari, N., et al. (2021). "Glucosamine-conjugated graphene quantum dots as versatile and pH-sensitive nanocarriers for enhanced delivery of curcumin targeting to breast cancer." Mater Sci Eng C Mater Biol Appl **121**: 111809.

Applying multifunctional nanocarriers, comprising specifically traceable and tumor targeting moieties, has significantly increased in cancer theranostics. Herein, a novel targeted, trackable, and pH-responsive drug delivery system was fabricated based on glucosamine (GlcN) conjugated graphene quantum dots (GQDs) loaded by hydrophobic anticancer agent, curcumin (Cur), to evaluate its targeting and cytotoxicity potential against breast cancer cells with overexpression of GlcN receptors. The biocompatible photoluminescent GQDs were synthesized from graphene oxide through the green and facile oxidizing method. The structural and spectral characterizations of the as-prepared GQDs and Cur/GlcN-GQDs were investigated. The GQDs sizes were within 20-30 nm and showed less than ten layers. A pH-sensitive and sustained release behavior was also observed for the Cur loaded nanocarrier with a total release of 37% at pH 5.5 and 17% at pH 7.4 after 150 h. In vitro cellular uptake studies through fluorescence microscopy and flow cytometry exhibited stronger fluorescence for the targeted nanocarrier against MCF-7 cells compared to the non-targeted one, owing to higher cellular internalization via GlcN receptor-mediated endocytosis. Furthermore, the MTT assay results demonstrated the nontoxicity of the bare nanocarrier with the cell viability of above 94% even at concentrations as high as 50 mug.ml(-1), while the Cur/GlcN-GQDs exhibited much more cytotoxicity against MCF-7 cells compared to Cur/GQDs. It is reasonable to conclude that this advanced multifunctional nano-assembly offers superior potential for breast cancer cell-targeted delivery.

Ghazani, A. A., et al. (2006). "High throughput quantification of protein expression of cancer antigens in tissue microarray using quantum dot nanocrystals." Nano Lett **6**(12): 2881-2886.

We developed and validated a novel method for quantifying protein expression of cancer tumors in an accurate, sensitive, and high throughput format. This technique integrates quantum dots, tissue microarray, optical spectroscopy, and algorithm design for analysis of tumor biopsies. The integration of this method for tissue analysis in the clinic bears potential impact for improving the diagnosis and treatment of cancer.

Ghoreishi, R. and M. Kia (2019). "Chemical reactivity and adsorption properties of pro-carbazine anti-cancer drug on gallium-doped nanotubes: a quantum chemical study." J Mol Model **25**(2): 46.

In this study, we propose new armchair single-walled nanotubes (SWNTs) for stable adsorption,

increasing drug delivery performance and decreasing side effects of pro-carbazine (Pro-CB) anti-cancer in the framework of B3LYP/6-31 g*/Lanl2DZ level of theory. Indeed, doping gallium (Ga) metal in SWNTs is naturally followed by changing of geometry, increasing dipole moment, and creating one site with high reactivity in order to better adsorption of the drug molecule. Chemical reactivity descriptors show that SWNTs and Pro-CB have electrophile and nucleophile roles in interaction, respectively. More importantly, high local and dual softness in Ga-doped SWNTs indicate improvement of drug adsorption. Parallel and perpendicular complexes result from their interaction in the N and the O sites. Negative values of binding energy (Ebind) show that composed complexes are energetically stable especially in the O site in comparison with the N site. On the other hand, more negative value of the Ebind in SWCNTs shows that these nanotubes are more effective for drug adsorption than their boron nitride counterparts. Graphical abstract The Ga dopping results in reducing of HOMO-LUMO gap and increasing charge transfer between SWNTs and Pro-CB, and formation better complex, especially SWCNT.

Gokarna, A., et al. (2008). "Quantum dot-based protein micro- and nanoarrays for detection of prostate cancer biomarkers." Proteomics **8**(9): 1809-1818.

In this article, we demonstrate the fabrication and detection of cancer protein biochips consisting of micro- and nanoarrays whereby pegylated quantum dots (QDs) conjugated to antibodies (Abs) of prostate specific antigens (PSA) were used for the detection of clinical biomarkers such as PSA. BSA which acts as an efficient blocking layer in microarrays, tends to show an interaction with QDs. In view of this fact, we investigated two series of samples which were fabricated in the presence and absence of BSA blocking layer. Variation in the incubation time required for the antigen-antibody interaction to take place, different proteins as controls and the effect of bare QDs on these microarrays, were the three main parameters which were studied in these two series. Samples fabricated in the absence of BSA blocking layer exhibited an extremely high specificity in the detection of cancer proteins and were also marked by negligible nonspecific binding effects of QDs, in stark contrast to the samples fabricated using BSA as a blocking layer. Fabrication of nanoarrays of QD-conjugated PSA Abs having a spot size of nearly 900 nm has also been demonstrated. Thus, we show the potential offered by QDs in in vitro analysis of cancer biomarker imaging.

Golsanamlou, Z., et al. (2021). "Sensing and bioimaging of lead ions in intracellular cancer cells and biomedical media using amine-functionalized silicon quantum dots fluorescent probe." Spectrochim Acta A Mol Biomol Spectrosc **256**: 119747.

A novel amine-functionalized silica quantum dots (SiQDs) fluorescent nanoprobe was developed for sensing of lead concentration in water, plasma and cell lysate. In addition, the developed probe was utilized for bioimaging of intracellular lead ions in HT 29 cancer cells. The amine-functionalized nanoprobe exhibited fluorescence emission at 445 nm under excitation at 355 nm. Upon addition of lead ions, the fluorescence of SiQDs linearly enhanced from 50 ng/mL to 5 microg/mL and 50 ng/mL to 25 microg/mL for plasma and standard media, respectively. The synthesis and fabrication of this probe are simple and serves high sensitivity with a limit of detection down to around 20 ng/mL. In the presence of various molecular and ion interfering, reliable results are obtained, confirming the specificity of the nanoprobe for lead ion detection. Meanwhile, amine-functionalized SiQD-based nanoprobe exhibits excellent cell membrane-permeability and biocompatibility. Thus, this probe is utilized for lead tracing in HT 29 cancer live cells. Fluorescent microscopy results confirmed the attachment of the produced nanomaterials to the HT 29 cancer cells.

Gonda, K., et al. (2015). "Predictive diagnosis of the risk of breast cancer recurrence after surgery by single-particle quantum dot imaging." Sci Rep **5**: 14322.

In breast cancer, the prognosis of human epidermal growth factor receptor 2 (HER2)-positive patients (20-25%) has been dramatically improved by the clinical application of the anti-HER2 antibody drugs trastuzumab and pertuzumab. However, the clinical outcomes of HER2-negative cases with a poor prognosis have not improved, and novel therapeutic antibody drugs or diagnostic molecular markers of prognosis are urgently needed. Here, we targeted protease-activated receptor 1 (PAR1) as a new biomarker for HER2-negative patients. The developed anti-PAR1 antibody inhibited PAR1 activation by matrix metalloprotease 1 and thereby prevented cancer-cell migration and invasion. To estimate PAR1 expression levels in HER2-negative patient tissues using the antibody, user-friendly immunohistochemistry with fluorescence nanoparticles or quantum dots (QDs) was developed. Previously, immunohistochemistry with QDs was affected by tissue autofluorescence, making quantitative measurement extremely difficult. We significantly improved the quantitative sensitivity of immunohistochemistry with QDs by using an autofluorescence-subtracted image and single-QD imaging. The immunohistochemistry showed that PAR1 expression was strongly correlated with relapse-free survival time in HER2-negative breast cancer patients. Therefore, the developed anti-PAR1 antibody is a strong candidate for use as an anticancer

drug and a prognostic biomarker for HER2-negative patients.

Govindammal, M., et al. (2022). "Quantum chemical calculations, spectroscopic studies and molecular docking investigations of the anti-cancer drug quercitrin with B-RAF inhibitor." Heliyon **8**(5): e09539.

Quercitrin is an anti-lung cancer agent. It is a naturally occurring flavonoid and its derivatives are mainly present in nuts and beverages. It is mainly available as a glycoside, and the quercitrin glycosides are found to prevent the metastasis of cancer. Quercitrin is optimized with 6-311++G(d,p) basis set using the B3LYP method to attain its minimum energy structure. The vibrational studies of the Quercitrin compound were elucidated with reference to Potential Energy Distribution (PED). The geometrical parameters were obtained and correlated with experimental values. To examine the nature of the charge transfer mechanism of Quercitrin, the HOMO-LUMO energy gap is computed. The anti-cancer activity of Quercitrin has been explored using molecular docking study that are used to estimate how the ligand interacts with protein, specifically to identify the best-fit orientation of the ligand, its binding mode, and intermolecular interactions of amino acid residues in the binding region of B-RAF kinase protein. The binding affinity of the compound Quercitrin (-7.14 kcal/mol) was found using AutoDock and validated with a Glide XP score in Schrodinger tool (-8.01 kcal/mol). MD simulations of protein-ligand complexes were monitored for 100 ns, from which the RMSD, RMSF, Rg, H-bonds, and interaction energy calculations were executed. From these investigations, it is identified that the compound quercitrin has maintained good structural stability, compactness, higher Hydrogen bonds, and interaction energies than the Imidazopyridinyl benzamide inhibitor.

Guo, R., et al. (2015). "Rhodamine-Functionalized Graphene Quantum Dots for Detection of Fe(3+) in Cancer Stem Cells." ACS Appl Mater Interfaces **7**(43): 23958-23966.

A turn-on orange-red fluorescent nanosensor based on rhodamine B derivative-functionalized graphene quantum dots (RBD-GQDs) has been successfully synthesized for Fe(3+) detection with high sensitivity and selectivity. By connecting with GQDs, the water solubility, sensitivity, photostability, and biocompatibility of RBD are drastically improved. The most distinctive feature of the RBD-GQDs, which sets them apart from other previously reported fluorophores or GQDs, is that they with the detection limits as low as 0.02 muM are demonstrated as a Fe(3+) turn-on fluorescent nanosensor in cancer stem cells. Fe(3+) binding to such GQDs (RBD-GQDs-Fe(3+)) with orange-red fluorescence of 43% quantum yield were demonstrated to be the biomarkers for cancer stem cell imaging.

Guo, W., et al. (2017). "Multifunctional Theranostic Agent of Cu2(OH)PO4 Quantum Dots for Photoacoustic Image-Guided Photothermal/Photodynamic Combination Cancer Therapy." ACS Appl Mater Interfaces **9**(11): 9348-9358.

Image-guided phototherapy is considered to be a prospective technique for cancer treatment because it can provide both oncotherapy and bioimaging, thus achieving an optimized therapeutic efficacy and higher treatment accuracy. Compared to complicated systems with multiple components, using a single material for this multifunctional purpose is preferable. In this work, we strategically fabricated poly(acrylic acid)- (PAA-) coated Cu2(OH)PO4 quantum dots [denoted as Cu2(OH)PO4@PAA QDs], which exhibit a strong near-infrared photoabsorption ability. As a result, an excellent photothermal conversion ability and the photoactivated formation of reactive oxygen species could be realized upon NIR irradiation, concurrently meeting the basic requirements for photothermal and photodynamic therapies. Moreover, phototherapeutic investigations on both cervical cancer cells in vitro and solid tumors of an in vivo mice model illustrated the effective antitumor effects of Cu2(OH)PO4@PAA upon 1064-nm laser irradiation, with no detectable lesions in major organs during treatment. Meanwhile, Cu2(OH)PO4@PAA is also an exogenous contrast for photoacoustic tomography (PAT) imaging to depict tumors under NIR irradiation. In brief, the Cu2(OH)PO4@PAA QDs prepared in this work are expected to serve as a multifunctional theranostic platform.

Habiba, K., et al. (2016). "Improving cytotoxicity against cancer cells by chemo-photodynamic combined modalities using silver-graphene quantum dots nanocomposites." Int J Nanomedicine **11**: 107-119.

The combination of chemotherapy and photodynamic therapy has emerged as a promising strategy for cancer therapy due to its synergistic effects. In this work, PEGylated silver nanoparticles decorated with graphene quantum dots (Ag-GQDs) were tested as a platform to deliver a chemotherapy drug and a photosensitizer, simultaneously, in chemo-photodynamic therapy against HeLa and DU145 cancer cells in vitro. Ag-GQDs have displayed high efficiency in delivering doxorubicin as a model chemotherapy drug to both cancer cells. The Ag-GQDs exhibited a strong antitumor activity by inducing apoptosis in cancer cells without affecting the viability of normal cells. Moreover, the Ag-GQDs exhibited a cytotoxic effect due to the generation of the reactive singlet oxygen upon

425 nm irradiation, indicating their applicability in photodynamic therapy. In comparison with chemo or photodynamic treatment alone, the combined treatment of Ag-GQDs conjugated with doxorubicin under irradiation with a 425 nm lamp significantly increased the death in DU145 and HeLa. This study suggests Ag-GQDs as a multifunctional and efficient therapeutic system for chemo-photodynamic modalities in cancer therapy.

Haldavnekar, R., et al. (2022). "Cancer Stem Cell DNA Enabled Real-Time Genotyping with Self-Functionalized Quantum Superstructures-Overcoming the Barriers of Noninvasive cfDNA Cancer Diagnostics." Small Methods **6**(4): e2101467.

Cancer diagnosis and determining its tissue of origin are crucial for clinical implementation of personalized medicine. Conventional diagnostic techniques such as imaging and tissue biopsy are unable to capture the dynamic tumor landscape. Although circulating tumor DNA (ctDNA) shows promise for diagnosis, the clinical relevance of ctDNA remains largely undetermined due to several biological and technical complexities. Here, cancer stem cell-ctDNA is used to overcome the biological complexities like the inability for molecular analysis of ctDNA and dependence on ctDNA concentration rather than the molecular profile. Ultrasensitive quantum superstructures overcome the technical complexities of trace-level detection and rapid diagnosis to detect ctDNA within its short half-life. Activation of multiple surface enhanced Raman scattering mechanisms of the quantum superstructures achieved a very high enhancement factor (1.35 x 10(11)) and detection at ultralow concentration (10(-15) M) with very high reliability (RSD: 3-12%). Pilot validation with clinical plasma samples from an independent validation cohort achieved a diagnosis sensitivity of approximately 95% and specificity of 83%. Quantum superstructures identified the tissue of origin with approximately 75-86% sensitivity and approximately 92-96% specificity. With large scale clinical validation, the technology can develop into a clinically useful liquid biopsy tool improving cancer diagnostics.

Haldavnekar, R., et al. (2018). "Non plasmonic semiconductor quantum SERS probe as a pathway for in vitro cancer detection." Nat Commun **9**(1): 3065.

Surface-enhanced Raman scattering (SERS)-based cancer diagnostics is an important analytical tool in early detection of cancer. Current work in SERS focuses on plasmonic nanomaterials that suffer from coagulation, selectivity, and adverse biocompatibility when used in vitro, limiting this research to stand-alone biomolecule sensing. Here we introduce a label-free, biocompatible, ZnO-based, 3D semiconductor quantum probe as a pathway for in vitro diagnosis of cancer. By reducing size of the probes to quantum scale, we observed a unique phenomenon of exponential increase in the SERS enhancement up to ~10(6) at nanomolar concentration. The quantum probes are decorated on a nano-dendrite platform functionalized for cell adhesion, proliferation, and label-free application. The quantum probes demonstrate discrimination of cancerous and non-cancerous cells along with biomolecular sensing of DNA, RNA, proteins and lipids in vitro. The limit of detection is up to a single-cell-level detection.

Hameroff, S. R. (2004). "A new theory of the origin of cancer: quantum coherent entanglement, centrioles, mitosis, and differentiation." Biosystems **77**(1-3): 119-136.

Malignant cells are characterized by abnormal segregation of chromosomes during mitosis ("aneuploidy"), generally considered a result of malignancy originating in genetic mutations. However, recent evidence supports a century-old concept that maldistribution of chromosomes (and resultant genomic instability) due to abnormalities in mitosis itself is the primary cause of malignancy rather than a mere byproduct. In normal mitosis chromosomes replicate into sister chromatids which are then precisely separated and transported into mirror-like sets by structural protein assemblies called mitotic spindles and centrioles, both composed of microtubules. The elegant yet poorly understood ballet-like movements and geometric organization occurring in mitosis have suggested guidance by some type of organizing field, however neither electromagnetic nor chemical gradient fields have been demonstrated or shown to be sufficient. It is proposed here that normal mirror-like mitosis is organized by quantum coherence and quantum entanglement among microtubule-based centrioles and mitotic spindles which ensure precise, complementary duplication of daughter cell genomes and recognition of daughter cell boundaries. Evidence and theory supporting organized quantum states in cytoplasm/nucleoplasm (and quantum optical properties of centrioles in particular) at physiological temperature are presented. Impairment of quantum coherence and/or entanglement among microtubule-based mitotic spindles and centrioles can result in abnormal distribution of chromosomes, abnormal differentiation and uncontrolled growth, and account for all aspects of malignancy. New approaches to cancer therapy and stem cell production are suggested via non-thermal laser-mediated effects aimed at quantum optical states of centrioles.

Han, S., et al. (2013). "[Application of functional quantum dots in cancer diagnosis and therapy: a

review]." Sheng Wu Gong Cheng Xue Bao **29**(1): 10-20.

Quantum dots (QDs) are nanometer-sized luminescent semiconductor nanocrystals. Their unique optical properties, such as high brightness, long-term stability, simultaneous detection of multiple signals and tunable emission spectra, make them appealing as potential diagnostic and therapeutic systems in oncology. Preparing the functional QDs by modifying bio-molecules such as antibody will have potential value for cancer diagnosis and treatment. This paper summarized the recent progress of promising application of QDs in cancer diagnosis and therapy, from identifying molecular targets, to drug delivery and therapy; from limitations of toxicity issues related to QDs in living organisms to multifunctional design and development. Finally, the promising applications of QDs are also discussed.

Han, S. J., et al. (2014). "Specific intracellular uptake of herceptin-conjugated CdSe/ZnS quantum dots into breast cancer cells." Biomed Res Int **2014**: 954307.

Herceptin, a typical monoclonal antibody, was immobilized on the surface of CdSe/ZnS core-shell quantum dots (QDs) to enhance their specific interactions with breast cancer cells (SK-BR3). The mean size of the core-shell quantum dots (28 nm), as determined by dynamic light scattering, increased to 86 nm after herceptin immobilization. The in vitro cell culture experiment showed that the keratin forming cancer cells (KB) proliferated well in the presence of herceptin-conjugated QDs (QD-Her, 5 nmol/mL), whereas most of the breast cancer cells (SK-BR3) had died. To clarify the mechanism of cell death, the interaction of SK-BR3 cells with QD-Her was examined by confocal laser scanning microscopy. As a result, the QD-Her bound specifically to the membrane of SK-BR3, which became almost saturated after 6 hours incubation. This suggests that the growth signal of breast cancer cells is inhibited completely by the specific binding of herceptin to the Her-2 receptor of SK-BR3 membrane, resulting in cell death.

Hasanzadeh, M. and N. Shadjou (2017). "What are the reasons for low use of graphene quantum dots in immunosensing of cancer biomarkers?" Mater Sci Eng C Mater Biol Appl **71**: 1313-1326.

Graphene quantum dots-based immunosensors have recently gained importance for detecting antigens and biomarkers responsible for cancer diagnosis. This paper reports a literature survey of the applications of graphene quantum dots for sensing cancer biomarkers. The survey sought to explore three questions: (1) Do graphene quantum dots improve immunosensing technology? (2) If so, can graphene quantum dots have a critical, positive impact on construction of immuno-devices? And (3) What is the reason for some troubles in the application of this technology? The number of published papers in the field seems positively answer the first two questions. However additional efforts must be made to move from the bench to the real diagnosis. Some approaches to improve the analytical performance of graphene quantum dots-based immunosensors through their figures of merit have been also discussed.

Hasanzadeh, M., et al. (2018). "An innovative immunosensor for ultrasensitive detection of breast cancer specific carbohydrate (CA 15-3) in unprocessed human plasma and MCF-7 breast cancer cell lysates using gold nanospear electrochemically assembled onto thiolated graphene quantum dots." Int J Biol Macromol **114**: 1008-1017.

The accurate quantification of the level of breast cancer specific protein CA 15-3 in serum is crucial for cancer prognosis. This work, a novel and sensitive label-free immunoassay based on gold nanospear (Au NSs) electrochemically assembled onto thiolated graphene quantum dots (CysA/GQDs) for the detection of CA 15-3 antibodies. The CysA/Au NSs/GQDs hybrid interface provides a large surface area for the effective immobilization of CA 15-3 antigens, as well as it ascertains the bioactivity and stability of immobilized CA 15-3 antigens. Field emission scanning electron microscope (FE-SEM), and EDS photoelectron spectroscopies were used to monitor the sensor fabrication. Also, cyclic voltammetry was used to quantify the extent of Au NSs' surface coverage by CA 15-3 antigens. Square wave voltammetry (SWV) was employed to investigate the immunosensor fabrication and to monitor the binding events between CA 15-3 antigens-antibodies. Under optimized experimental conditions, the immunosensor displayed good sensitivity and specificity. The CA 15-3 were detected in a concentration as low as 0.11U/mL with a linear range from 0.16-125U/mL. The high sensitivity of the immunosensor may derive from the high loading of CA 15-3 antibodies on CysA/Au NSs/GQDs hybrid interface which increases the number of binding events. The method was successfully applied assay of the CA 15-3 in unprocessed human plasma samples. Also, proposed immunosensor was applied to the assay of CA 15-3 malignant cell line lysates (human breast adenocarcinoma cell line-MCF-7).

Hashemkhani, M., et al. (2021). "Cetuximab-Ag2S quantum dots for fluorescence imaging and highly effective combination of ALA-based photodynamic/chemo-therapy of colorectal cancer cells." Nanoscale **13**(35): 14879-14899.

Colorectal cancer (CRC) has a poor prognosis and urgently needs better therapeutic approaches. 5-Aminolevulinic acid (ALA) induced protoporphyrin IX

(PpIX) based photodynamic therapy (PDT) is already used in the clinic for several cancers but not yet well investigated for CRC. Currently, systemic administration of ALA offers a limited degree of tumour selectivity, except for intracranial tumours, limiting its wider use in the clinic. The combination of effective ALA-PDT and chemotherapy may provide a promising alternative approach for CRC treatment. Herein, theranostic Ag2S quantum dots (AS-2MPA) optically trackable in near-infrared (NIR), conjugated with endothelial growth factor receptor (EGFR) targeting Cetuximab (Cet) and loaded with ALA for PDT monotherapy or ALA/5-fluorouracil (5FU) for the combination therapy are proposed for enhanced treatment of EGFR(+) CRC. AS-2MPA-Cet exhibited excellent targeting of the high EGFR expressing cells and showed a strong intracellular signal for NIR optical detection in a comparative study performed on SW480, HCT116, and HT29 cells, which exhibit high, medium and low EGFR expression, respectively. Targeting provided enhanced uptake of the ALA loaded nanoparticles by strong EGFR expressing cells and formation of higher levels of PpIX. Cells also differ in their efficiency to convert ALA to PpIX, and SW480 was the best, followed by HT29, while HCT116 was determined as unsuitable for ALA-PDT. The therapeutic efficacy was evaluated in 2D cell cultures and 3D spheroids of SW480 and HT29 cells using AS-2MPA with either electrostatically loaded, hydrazone or amide linked ALA to achieve different levels of pH or enzyme sensitive release. Most effective phototoxicity was observed in SW480 cells using AS-2MPA-ALA-electrostatic-Cet due to enhanced uptake of the particles, fast ALA release and effective ALA-to-PpIX conversion. Targeted delivery reduced the effective ALA concentration significantly which was further reduced with codelivery of 5FU. Delivery of ALA via covalent linkages was also effective for PDT, but required a longer incubation time for the release of ALA in therapeutic doses. Phototoxicity was correlated with high levels of reactive oxygen species (ROS) and apoptotic/necrotic cell death. Hence, both AS-2MPA-ALA-Cet based PDT and AS-2MPA-ALA-Cet-5FU based chemo/PDT combination therapy coupled with strong NIR tracking of the nanoparticles demonstrate an exceptional therapeutic effect on CRC cells and excellent potential for synergistic multistage tumour targeting therapy.

Havanur, S., et al. (2019). "Poly(N,N-diethyl acrylamide)/functionalized graphene quantum dots hydrogels loaded with doxorubicin as a nano-drug carrier for metastatic lung cancer in mice." Mater Sci Eng C Mater Biol Appl **105**: 110094.

Cancer has emanated as a daunting menace to human-kind even though medicine, science, and technology has reached its zenith. Subsequent scarcity in the revelation of new drugs, the exigency of salvaging formerly discovered toxic drugs such as doxorubicin has emerged. The invention of drug carrier has made drug delivery imminent which is ascribable to its characteristic traits of specific targeting, effective response to stimuli and biocompatibility. In this paper, the nanoscale polymeric drug carrier poly(N,N-diethyl acrylamide) nanohydrogel has been synthesized by inverse emulsion polymerization. Lower critical solution temperature of the polymeric carrier has been modified using graphene quantum. The particle size of pure nanohydrogel was in the range of 47 to 59.5nm, and graphene quantum dots incorporated nanohydrogels was in the range of 68.1 to 87.5nm. Doxorubicin (hydroxyl derivative of anthracycline) release behavior as a function of time and temperature was analyzed, and the Lower critical solution temperature of the synthesized nanohydrogels has been found to be in the range of 28-42 degrees C. Doxorubicin release characteristics have improved significantly as the surrounding temperature of the release media was increased near to physiological temperature. Further, the cumulative release profile was fitted in the different kinetic model and found to follow a Fickian diffusion release mechanism. The hydrogel was assessed for its cytotoxicity in B16F10 cells by MTT assay. In-vivo studies were done to study the lung metastasis by melanoma cancer and the results showed a rational favorable prognosis which was confirmed by evaluating hematological parameters and the non-immunogenic nature of nanohydrogel by cytokine assay. Comprehensively, the results suggested that poly(N,N-diethyl acrylamide) nanohydrogels have potential application as an intelligent drug carrier for melanoma cancer.

He, H., et al. (2022). "Bioadhesive injectable hydrogel with phenolic carbon quantum dot supported Pd single atom nanozymes as a localized immunomodulation niche for cancer catalytic immunotherapy." Biomaterials **280**: 121272.

Immunotherapy is a powerful way to treat cancer, however, systemic treatment-associated adverse effects remain a major concern. In this study, a bioadhesive injectable hydrogel is developed to provide localized immune niches for tumor microenvironment immunomodulation and cancer catalytic immunotherapy. First, a phenolic single atom nanozyme (SAN) was developed by in situ synthesis of Pd single atom on catechol-grafted carbon-quantum-dot (DA-CQD@Pd) templates. Then, the bioadhesive injectable hydrogel consisting of DA-CQD@Pd SAN and immune adjuvant CpGODN was formed through SAN-catalyzed free-radical polymerization. The SAN exhibited peroxidase-like activity to generate ROS and kill tumor cells through catalytic therapy. The hydrogel locally

released CpGODN in a sustained manner, which limited the risk of systemic exposure, reducing the impact of CpGODN toxicity, and protecting CpGODN from degradation. The bioadhesive hydrogel immobilized around solid tumor to provide an immune response site after injection. When combined it with the administration of immune checkpoint inhibitor anti-PD-L1, the hydrogel realized localized immunomodulation, maximized therapeutic efficacy and prevents tumor metastasis via a catalytic immunotherapy.

He, S. J., et al. (2016). "CdSe/ZnS quantum dots induce photodynamic effects and cytotoxicity in pancreatic cancer cells." World J Gastroenterol **22**(21): 5012-5022.

AIM: To investigate the photodynamic effect of CdSe/ZnS quantum dots (QDs) on pancreatic cancer cells and elucidate the probable mechanisms. METHODS: The pancreatic cancer cell line SW1990 was treated with different concentrations of CdSe/ZnS QDs (0, 0.5, 1.0, 1.5, 2.0, 2.5 mumol/L), with or without illumination. The viability of SW1990 cells was tested using the Cell Counting Kit-8 (CCK-8) assay. The ultrastructural changes of SW1990 cells were observed by transmission electron microscopy. Apoptosis was detected by nuclear staining and flow cytometry (FCM). Reactive oxygen species (ROS) were measured by dichlorofluorescein diacetate via fluorescence microscopy. Expression of Bax, Bcl-2 and caspase-3 was measured by real-time polymerase chain reaction (PCR) and protein immunoblotting 24 h after SW1990 cells were treated with CdSe/ZnS QDs and illuminated. RESULTS: The CCK-8 assay results showed that both CdSe/ZnS QDs with and without illumination suppressed SW1990 cell proliferation. Cell viability was significantly lower when illuminated or with a longer incubation time and a higher light dose. CdSe/ZnS QDs with illumination caused ultrastructural changes in SW1990 cells, such as organelle degeneration and chromatin condensation and aggregation at the periphery of the nucleus. Fluorescence microscopy and FCM showed that CdSe/ZnS QDs (1.5 mumol/L) with illumination increased SW1990 cell apoptosis (53.2%) and ROS generation compared with no illumination. Real-time PCR showed that expression of Bax and caspase-3 was upregulated and Bcl-2 was downregulated. Immunoblotting results were consistent with real-time PCR results. Inhibition of ROS and apoptosis both attenuated QD-photodynamic-therapy-induced cell death. CONCLUSION: CdSe/ZnS QDs can be used as a photosensitizer to inhibit SW1990 cell proliferation through ROS generation and apoptotic protein expression regulation.

He, Y., et al. (2011). "In situ spectral imaging of marker proteins in gastric cancer with near-infrared and visible quantum dots probes." Talanta **85**(1): 136-141.

This study presents the investigation of bioconjugating ability of near-infrared (NIR) CdSeTe/ZnS quantum dots (QDs) (710 nm) and visible CdSe QDs (595 nm) in immunofluorescent staining for cancer biomarkers in gastric cancer tissues probed with the homemade Hadamard transform (HT) spectral imaging microscope and a commercial multispectral imaging system. The results show that imunostaining ability of NIR QDs probes is stronger than that of visible QDs when the two kinds of QDs are simultaneously used to probe the cancer biomarkers such as cytokeratin 20 (CK20) and proliferating cell nuclear antigen (PCNA) in gastric cancer tissues. Moreover, when the two QDs probes are used for immunostaining successively for the same target molecules, staining order has great influences on the final results due to their different conjugating ability to the marker proteins. The results imply that NIR QDs hold more promise for real-time imaging of tumor tissues due to its higher sensitivity and contrast. In addition, the results also demonstrate the potential of Hadamard transform spectral imaging as a useful tool in biomedical analysis and quantitative evaluation for tumor tissues.

He, Y., et al. (2012). "Quantum dots-based immunofluorescent imaging of stromal fibroblasts Caveolin-1 and light chain 3B expression and identification of their clinical significance in human gastric cancer." Int J Mol Sci **13**(11): 13764-13780.

Caveolin-1 (Cav-1) expression deficiency and autophagy in tumor stromal fibroblasts (hereafter fibroblasts) are involved in tumor proliferation and progression, particularly in breast and prostate cancer. The aim of this study was to detect the expression of fibroblastic Cav-1 and LC3B, markers of autophagy, in gastric cancer (GC) and to analyze their clinical significances. Furthermore, because Epstein-Barr virus (EBV)-associated GC (EBVaGC) is a unique subtype of GC; we compared the differential expression of fibroblastic Cav-1 and LC3B in EBVaGC and non-EBVaGC. Quantum dots (QDs)-based immunofluorescence histochemistry was used to examine the expression of fibroblastic Cav-1 and LC3B in 118 cases of GC with adequate stroma. QDs-based double immunofluorescence labeling was performed to detect the coexpression of Cav-1 and LC3B proteins. EBV-encoded small RNA was detected by QDs-based fluorescence in situ hybridization to identify EBVaGC. Multivariate analysis indicated that low fibroblastic Cav-1 level was an independent prognosticator ($p = 0.029$) that predicted poorer survival of GC patients. Positive fibroblastic LC3B was correlated with lower invasion ($p = 0.032$) and was positively associated with Cav-1 expression ($r = 0.432$, $p < 0.001$). EBV infection did not affect fibroblastic Cav-1 and LC3B expression. In conclusion, positive fibroblastic LC3B correlates

with lower invasion, and low expression of fibroblastic Cav-1 is a novel predictor of poor GC prognosis.

Helle, M., et al. (2012). "Visualisation of sentinel lymph node with indium-based near infrared emitting Quantum Dots in a murine metastatic breast cancer model." PLoS One **7**(8): e44433.

Due to its non-invasiveness, high temporal resolution and lower cost, fluorescence imaging is an interesting alternative to the current method (blue dye and radiocolloid) of sentinel lymph node (SLN) mapping in breast cancer. Near-infrared (NIR) emitting cadmium-based Quantum Dots (QDs) could be used for this purpose; however, their wide application is limited because of the toxicity of heavy metals composing the core. Our recent work demonstrated that indium-based QDs exhibit a weak acute local toxicity in vivo compared to their cadmium-based counterparts. In the present study we confirmed the weak toxicity of CuInS(2)/ZnS QDs in different in vitro models. Further in vivo studies in healthy mice showed that In-based QDs could be visualised in SLN in a few minutes after administration with a progressive increase in fluorescence until 8 h. The quantity of indium was assessed in selected organs and tissues by inductively coupled plasma - mass spectroscopy (ICP-MS) as a function of post-injection time. QD levels decrease rapidly at the injection point in the first hours after administration with a parallel increase in the lymph nodes and to a lesser extent in the liver and spleen. In addition, we observed that 3.5% of the injected indium dose was excreted in faeces in the first 4 days, with only trace quantities in the urine. Metastatic spread to the lymph nodes may hamper its visualisation. Therefore, we further performed non-invasive fluorescence measurement of QDs in SLN in tumour-bearing mice. Metastatic status was assessed by immunohistology and molecular techniques and revealed the utmost metastatic invasion of 36% of SLN. Fluorescence signal was the same irrespective of SLN status. Thus, near-infrared emitting cadmium-free QDs could be an excellent SLN tracer.

Hernando, P. J., et al. (2021). "Recent Developments in the Use of Glyconanoparticles and Related Quantum Dots for the Detection of Lectins, Viruses, Bacteria and Cancer Cells." Front Chem **9**: 668509.

Carbohydrate-coated nanoparticles-glyconanoparticles-are finding increased interest as tools in biomedicine. This compilation, mainly covering the past five years, comprises the use of gold, silver and ferrite (magnetic) nanoparticles, silicon-based and cadmium-based quantum dots. Applications in the detection of lectins/protein toxins, viruses and bacteria are covered, as well as advances in detection of cancer cells. The role of the carbohydrate moieties in stabilising nanoparticles and providing selectivity in bioassays is discussed, the issue of cytotoxicity encountered in some systems, especially semiconductor quantum dots, is also considered. Efforts to overcome the latter problem by using other types of nanoparticles, based on gold or silicon, are also presented.

Hoyos, F. T., et al. (2019). "Study of cervical cancer through fractals and a method of clustering based on quantum mechanics." Appl Radiat Isot **150**: 182-191.

Tumor growth in the cervix is a complex process. Understanding this phenomena is quite relevant in order to establish proper diagnosis and therapy strategies and a possible startpoint is to evaluate its complexity through the scaling analysis, which define the tumor growth geometry. In this work, tumor interface from primary tumors of squamous cells and adenocarcinomas for cervical cancer were extracted. Fractal dimension and local roughness exponent (Barabasi and Stanley (1996)), alphaloc, were calculated to characterize the in vivo 3-D tumor growth. Image acquisition was carried out according to the standard protocol used for cervical cancer radiotherapy, i.e., axial, magnetic resonance T1 - weighted contrast enhanced images comprising the cervix volume for image registration. Image processing was carried out by a classification scheme based on quantum clustering algorithm (Mussa et al. (2015)) combined with the application of the K-means procedure upon contrasted images (Demirkaya et al. (2008)). The results show significant variations of the parameters depending on the tumor stage and its histological origin.

Hu, K., et al. (2015). "In Vivo Cancer Dual-Targeting and Dual-Modality Imaging with Functionalized Quantum Dots." J Nucl Med **56**(8): 1278-1284.

UNLABELLED: Semiconductor quantum dots (QDs), after surface modification to provide water solubility and biocompatibility, have a promising future in biomedical applications. In this study, a dual receptor-targeting dual-modality PET/near-infrared fluorescence (NIRF) probe was developed for accurate assessment of the pharmacokinetics and tumor-targeting efficacy of QDs. METHODS: QDs were modified by beta-Glu-RGD-BBN (RGD is arginine-glycine-aspartate acid, and BBN is bombesin) peptides and then labeled with (18)F via the 4-nitrophenyl-2-(18)F-fluoropropionate prosthetic group. Cytotoxicity and cell-binding assay of QD-RGD-BBN were performed with PC-3 cells. In vivo dual-modality PET/NIRF imaging of prostate tumor-bearing mice was investigated using QD-RGD-BBN and 2-(18)F-fluoropropionyl-QD-RGD-BBN ((18)F-FP-QD-RGD-BBN). An in vivo biodistribution study of (18)F-FP-QD-RGD-BBN was performed on normal mice. RESULTS: QD-RGD-BBN exhibited strong red luminescence (600-800 nm) with the same maximum

fluorescence wavelength (705 nm) as QD705 and slightly lower toxicity than that of QD705 in PC-3 cells at concentrations of greater than 30 mug/mL. Uptake of QD-RGD-BBN in PC-3 cells showed no significant decrease in the presence of an excess amount of dimer arginine-glycine-aspartate acid (RGD2) or bombesin(7-14) (BBN) peptide but was blocked significantly in the presence of an excess amount of NH2-RGD-BBN. Dual-function PET/NIRF imaging is able to accurately assess the biodistribution and tumor-targeting efficacy of the (18)F-labeled functionalized QDs. CONCLUSION: The functionalized QD probe has great potential as a universal dual-targeting probe for detecting tumors in living subjects, opening up a new strategy for the development of multitargeting multimodality (18)F-labeled QD probes with improved tumor-targeting efficacy.

Hu, M., et al. (2010). "Ultrasensitive, multiplexed detection of cancer biomarkers directly in serum by using a quantum dot-based microfluidic protein chip." ACS Nano **4**(1): 488-494.

Sensitive and selective detection for cancer biomarkers are critical in cancer clinical diagnostics. Here we developed a microfluidic protein chip for an ultrasensitive and multiplexed assay of cancer biomarkers. Aqueous-phase-synthesized CdTe/CdS quantum dots (aqQDs) were employed as fluorescent signal amplifiers to improve the detection sensitivity. Secondary antibodies (goat anti-mouse IgG) were conjugated to luminescent CdTe/CdS QDs to realize a versatile fluorescent probe that could be used for multiplexed detection in both sandwich and reverse phase immunoassays. We found that our microfluidic protein chip not only possessed ultrahigh femtomolar sensitivity for cancer biomarkers, but was selective enough to be directly used in serum. This protein chip thus combines the high-throughput capabilities of a microfluidic network with the high sensitivity and multicolor imaging ability offered by highly fluorescent QDs, which can become a promising diagnostic tool in clinical applications.

Hu, P., et al. (2011). "Multiplexed quantum dot labeling of activated c-Met signaling in castration-resistant human prostate cancer." PLoS One **6**(12): e28670.

The potential application of multiplexed quantum dot labeling (MQDL) for cancer detection and prognosis and monitoring therapeutic responses has attracted the interests of bioengineers, pathologists and cancer biologists. Many published studies claim that MQDL is effective for cancer biomarker detection and useful in cancer diagnosis and prognosis, these studies have not been standardized against quantitative biochemical and molecular determinations. In the present study, we used a molecularly characterized human prostate cancer cell model exhibiting activated c-Met signaling with epithelial to mesenchymal transition (EMT) and lethal metastatic progression to bone and soft tissues as the gold standard, and compared the c-Met cell signaling network in this model, in clinical human prostate cancer tissue specimens and in a castration-resistant human prostate cancer xenograft model. We observed c-Met signaling network activation, manifested by increased phosphorylated c-Met in all three. The downstream survival signaling network was mediated by NF-kappaB and Mcl-1 and EMT was driven by receptor activator of NF-kappaB ligand (RANKL), at the single cell level in clinical prostate cancer specimens and the xenograft model. Results were confirmed by real-time RT-PCR and western blots in a human prostate cancer cell model. MQDL is a powerful tool for assessing biomarker expression and it offers molecular insights into cancer progression at both the cell and tissue level with high degree of sensitivity.

Hu, Z., et al. (2016). "Biomarker quantification by multiplexed quantum dot technology for predicting lymph node metastasis and prognosis in head and neck cancer." Oncotarget **7**(28): 44676-44685.

PURPOSE: To predict lymph node metastasis and prognosis in head and neck squamous cell carcinoma (HNSCC). RESULTS: The combination of membranous E-cadherin and membranous epidermal growth factor receptor (EGFR) quantified by QD technology with age, gender, and grade had greater predictive power than any of the single biomarkers or the two combined biomarkers quantified by conventional immunohistochemistry (IHC). The predictive power of this model was validated in another independent sample set; the predictive sensitivity of this model for LNM was 87.5%, with specificity up to 97.4%, and accuracy 92.9%. Furthermore, a higher membranous E-cadherin level was significantly correlated with better overall and disease-free survival (OS, DFS; P = 0.002, 0.033, respectively), while lower cytoplasmic vimentin and membranous EGFR levels were significantly correlated with better OS (P = 0.016 and 0.021, respectively). The combined biomarkers showed a stronger prognostic value for OS and DFS than any of the single biomarkers. METHODS: Multiplexed quantum dots (QDs) were used to simultaneously label E-cadherin, vimentin, and EGFR with beta-actin as an internal control. Primary tissue samples from 97 HNSCC patients, 49 with and 48 without LNM were included in the training set. Levels of membranous E-cadherin, cytoplasmic vimentin, and membranous EGFR were quantified by InForm software and correlated with clinical characteristics. CONCLUSIONS: Multiplexed subcellular QD quantification of EGFR and E-cadherin is a potential

strategy for the prediction of LNM, DFS, and OS of HNSCC patients.

Hua, X., et al. (2013). "Selective collection and detection of MCF-7 breast cancer cells using aptamer-functionalized magnetic beads and quantum dots based nano-bio-probes." Anal Chim Acta **788**: 135-140.

A novel strategy for selective collection and detection of breast cancer cells (MCF-7) based on aptamer-cell interaction was developed. Mucin 1 protein (MUC1) aptamer (Apt1) was covalently conjugated to magnetic beads to capture MCF-7 cell through affinity interaction between Apt1 and MUC1 protein that overexpressed on the surface of MCF-7 cells. Meanwhile, a nano-bio-probe was constructed by coupling of nucleolin aptamer AS1411 (Apt2) to CdTe quantum dots (QDs) which were homogeneously coated on the surfaces of monodispersed silica nanoparticles (SiO2 NPs). The nano-bio-probe displayed similar optical and electrochemical performances to free CdTe QDs, and remained high affinity to nucleolin overexpressed cells through the interaction between AS1411 and nucleolin protein. Photoluminescence (PL) and square-wave voltammetric (SWV) assays were used to quantitatively detect MCF-7 cells. Improved selectivity was obtained by using these two aptamers together as recognition elements simultaneously, compared to using any single aptamer. Based on the signal amplification of QDs coated silica nanoparticles (QDs/SiO2), the detection sensitivity was enhanced and a detection limit of 201 and 85 cells mL(-1) by PL and SWV method were achieved, respectively. The proposed strategy could be extended to detect other cells, and showed potential applications in cell imaging and drug delivery.

Huang, D. H., et al. (2009). "Quantum dot-based quantification revealed differences in subcellular localization of EGFR and E-cadherin between EGFR-TKI sensitive and insensitive cancer cells." Nanotechnology **20**(22): 225102.

Nanoparticle quantum dots (QDs) provide sharper and more photostable fluorescent signals than organic dyes, allowing quantification of multiple biomarkers simultaneously. In this study, we quantified the expression of epidermal growth factor receptor (EGFR) and E-cadherin (E-cad) in the same cells simultaneously by using secondary antibody-conjugated QDs with two different emission wavelengths (QD605 and QD565) and compared the cellular distribution of EGFR and E-cad between EGFR-tyrosine kinase inhibitor (TKI)-insensitive and -sensitive lung and head and neck cancer cell lines. Relocalization of EGFR and E-cad upon treatment with the EGFR-TKI erlotinib in the presence of EGF was visualized and analyzed quantitatively. Our results showed that QD-immunocytochemistry (ICC)-based technology can not only quantify basal levels of multiple biomarkers but also track the localization of the biomarkers upon biostimulation. With this new technology we found that in EGFR-TKI-insensitive cells, EGFR and E-cad were located mainly in the cytoplasm; while in sensitive cells, they were found mainly on the cell membrane. After induction with EGF, both EGFR and E-cad internalized to the cytoplasm, but the internalization capability in sensitive cells was greater than that in insensitive cells. Quantification also showed that inhibition of EGF-induced EGFR and E-cad internalization by erlotinib in the sensitive cells was stronger than that in the insensitive cells. These studies demonstrate substantial differences between EGFR-TKI-insensitive and -sensitive cancer cells in EGFR and E-cad expression and localization both at the basal level and in response to EGF and erlotinib. QD-based analysis facilitates the understanding of the features of EGFR-TKI-insensitive versus -sensitive cancer cells and may be used in the prediction of patient response to EGFR-targeted therapy.

Huang, G., et al. (2019). "Involvement of ABC transporters in the efflux and toxicity of MPA-COOH-CdTe quantum dots in human breast cancer SK-BR-3 cells." J Biochem Mol Toxicol **33**(8): e22343.

This paper aimed to study the possible involvement of adenosine triphosphate-binding cassette (ABC) transporters in the detoxification of quantum dots (QDs) in human breast carcinoma (SK-BR-3) cells. The effects of QD sizes on such interactions were also evaluated. For this purpose, we used monodispersed MPA-COOH-CdTe QDs with different diameters (emission length at 560 and 625 nm, named as QD-560 and QD-625). Such QDs tended to accumulate in cells and cause significant toxicity. Using specific inhibitors of ABC transporters, the cellular accumulation and toxicity of QDs in SK-BR-3 cells were significantly affected. Moreover, treatment of QDs caused concentration- and time-dependent induction of ABC transporters. Furthermore, the induction effects of smaller QDs were found to be greater than larger ones at equivalent concentrations, suggesting a size-dependent recognition of substrates by ABC transporters. Overall, these results provided important support for the modulation of QDs toxicity by ABC transporters.

Huang, X., et al. (2021). "CKAP4 Antibody-Conjugated Si Quantum Dot Micelles for Targeted Imaging of Lung Cancer." Nanoscale Res Lett **16**(1): 124.

At present, various fluorescent nanomaterials have been designed and synthesized as optical contrast agents for surgical navigation. However, there have been no reports on the preparation of fluorescent contrast agents for lung cancer surgery navigation using

silicon quantum dots (Si QDs). This study improved and modified the water-dispersible Si QD micelles reported by Pi et al. to prepare Si QD micelles-CKAP4. The data showed that the Si QD micelles-CKAP4 were spherical particles with a mean hydrodiameter of approximately 78.8 nm. UV-visible absorption of the Si QD micelles-CKAP4 ranged from 200 to 500 nm. With an excitation wavelength of 330 nm, strong fluorescence at 640 nm was observed in the fluorescence emission spectra. Laser confocal microscopy and fluorescence microscopy assay showed that the Si QD micelles-CKAP4 exhibited good targeting ability to lung cancer cells and lung cancer tissues in vitro. The in vivo fluorescence-imaging assay showed that the Si QD micelles-CKAP4 was metabolized by the liver and excreted by the kidney. In addition, Si QD micelles-CKAP4 specifically targeted lung cancer tissue in vivo compared with healthy lung tissue. Cytotoxicity and hematoxylin and eosin staining assays showed that the Si QD micelles-CKAP4 exhibited high biosafety in vitro and in vivo. Si QD micelles-CKAP4 is a specifically targeted imaging agent for lung cancer and is expected to be a fluorescent contrast agent for lung cancer surgical navigation in the future.

Iannazzo, D., et al. (2021). "Recent Advances on Graphene Quantum Dots as Multifunctional Nanoplatforms for Cancer Treatment." Biotechnol J **16**(2): e1900422.

Graphene quantum dots (GQDs), the latest member of the graphene family, have attracted enormous interest in the last few years, due to their exceptional physical, chemical, electrical, optical, and biological properties. Their strong size-dependent photoluminescence and the presence of many reactive groups on the graphene surface allow their multimodal conjugation with therapeutic agents, targeting ligands, polymers, light responsive agents, fluorescent dyes, and functional nanoparticles, making them valuable agents for cancer diagnosis and treatment. In this review, the very recent advances covering the last 3 years on the applications of GQDs as drug delivery systems and theranostic tools for anticancer therapy are discussed, highlighting the relevant factors which regulate their biocompatibility. Among these factors, the size, kind, and degree of surface functionalization have shown to greatly affect their use in biological systems. Toxicity issues, which still represent an open challenge for the clinical development of GQDs based therapeutic agents, are also discussed at cellular and animal levels.

Iannazzo, D., et al. (2021). "Smart Biosensors for Cancer Diagnosis Based on Graphene Quantum Dots." Cancers (Basel) **13**(13).

The timely diagnosis of cancer represents the best chance to increase treatment success and to reduce cancer deaths. Nanomaterials-based biosensors containing graphene quantum dots (GQDs) as a sensing platform show great promise in the early and sensitive detection of cancer biomarkers, due to their unique chemical and physical properties, large surface area and ease of functionalization with different biomolecules able to recognize relevant cancer biomarkers. In this review, we report different advanced strategies for the synthesis and functionalization of GQDs with different agents able to selectively recognize and convert into a signal specific cancer biomarkers such as antigens, enzymes, hormones, proteins, cancer related byproducts, biomolecules exposed on the surface of cancer cells and changes in pH. The developed optical, electrochemical and chemiluminescent biosensors based on GQDs have been shown to ensure the effective diagnosis of several cancer diseases as well as the possibility to evaluate the effectiveness of anticancer therapy. The wide linear range of detection and low detection limits recorded for most of the reported biosensors highlight their great potential in clinics for the diagnosis and management of cancer.

Iannazzo, D., et al. (2019). "A Smart Nanovector for Cancer Targeted Drug Delivery Based on Graphene Quantum Dots." Nanomaterials (Basel) **9**(2).

Graphene quantum dots (GQD), the new generation members of graphene-family, have shown promising applications in anticancer therapy. In this study, we report the synthesis of a fluorescent and biocompatible nanovector, based on GQD, for the targeted delivery of an anticancer drug with benzofuran structure (BFG) and bearing the targeting ligand riboflavin (RF, vitamin B2). The highly water-dispersible nanoparticles, synthesized from multi-walled carbon nanotubes (MWCNT) by prolonged acidic treatment, were linked covalently to the drug by means of a cleavable PEG linker while the targeting ligand RF was conjugated to the GQD by pi(-)pi interaction using a pyrene linker. The cytotoxic effect of the synthesized drug delivery system (DDS) GQD-PEG-BFG@Pyr-RF was tested on three cancer cell lines and this effect was compared with that exerted by the same nanovector lacking the RF ligand (GQD-PEG-BFG) or the anticancer drug (GQD@Pyr-RF). The results of biological tests underlined the low cytotoxicity of the GQD sample and the cytotoxic activity of the DDS against the investigated cancer cell lines with a higher or similar potency to that exerted by the BFG alone, thus opening new possibilities for the use of this drug or other anticancer agents endowed of cytotoxicity and serious side effects.

Iannazzo, D., et al. (2017). "Graphene quantum dots for cancer targeted drug delivery." Int J Pharm **518**(1-2): 185-192.

A biocompatible and cell traceable drug delivery system Graphene Quantum Dots (GQD) based, for the targeted delivery of the DNA intercalating drug doxorubicin (DOX) to cancer cells, is here reported. Highly dispersible and water soluble GQD, synthesized by acidic oxidation and exfoliation of multi-walled carbon nanotubes (MWCNT), were covalently linked to the tumor targeting module biotin (BTN), able to efficiently recognize biotin receptors over-expressed on cancer cells and loaded with DOX. Biological test performed on A549 cells reported a very low toxicity of the synthesized carrier (GQD and GQD-BTN). In GQD-BTN-DOX treated cancer cells, the cytotoxicity was strongly dependent from cell uptake which was greater and delayed after treatment with GQD-BTN-DOX system with respect to what observed for cells treated with the same system lacking of the targeting module BTN (GQD-DOX) or with the free drug alone. A delayed nuclear internalization of the drug is reported, due to the drug detachment from the nanosystem, triggered by the acidic environment of cancer cells.

Iliyasu, A. M. and C. Fatichah (2017). "A Quantum Hybrid PSO Combined with Fuzzy k-NN Approach to Feature Selection and Cell Classification in Cervical Cancer Detection." Sensors (Basel) **17**(12).

A quantum hybrid (QH) intelligent approach that blends the adaptive search capability of the quantum-behaved particle swarm optimisation (QPSO) method with the intuitionistic rationality of traditional fuzzy k-nearest neighbours (Fuzzy k-NN) algorithm (known simply as the Q-Fuzzy approach) is proposed for efficient feature selection and classification of cells in cervical smeared (CS) images. From an initial multitude of 17 features describing the geometry, colour, and texture of the CS images, the QPSO stage of our proposed technique is used to select the best subset features (i.e., global best particles) that represent a pruned down collection of seven features. Using a dataset of almost 1000 images, performance evaluation of our proposed Q-Fuzzy approach assesses the impact of our feature selection on classification accuracy by way of three experimental scenarios that are compared alongside two other approaches: the All-features (i.e., classification without prior feature selection) and another hybrid technique combining the standard PSO algorithm with the Fuzzy k-NN technique (P-Fuzzy approach). In the first and second scenarios, we further divided the assessment criteria in terms of classification accuracy based on the choice of best features and those in terms of the different categories of the cervical cells. In the third scenario, we introduced new QH hybrid techniques, i.e., QPSO combined with other supervised learning methods, and compared the classification accuracy alongside our proposed Q-Fuzzy approach. Furthermore, we employed statistical approaches to establish qualitative agreement with regards to the feature selection in the experimental scenarios 1 and 3. The synergy between the QPSO and Fuzzy k-NN in the proposed Q-Fuzzy approach improves classification accuracy as manifest in the reduction in number cell features, which is crucial for effective cervical cancer detection and diagnosis.

Itchins, M. and N. Pavlakis (2022). "The quantum leap in therapeutics for advanced ALK+ non-small cell lung cancer and pursuit to cure with precision medicine." Front Oncol **12**: 959637.

Since the discovery 15 years ago, we have seen a quantum leap in the treatment and survival for individuals diagnosed with ALK+ lung cancers. Unfortunately however, for most, the diagnosis is made in an incurable circumstance given the late presentation of symptoms. Through a revolutionary wave of therapeutics, individuals may remarkably live over a decade, however many fall short of this milestone, as the molecular profile of this disease is very heterogeneous, reflected in variable survival outcomes. Despite a significant improval in survival and quality of life with ALK-inhibitor monotherapies, now available across multiple-generations, drug resistance and disease relapse remains inevitable, and treatment is offered in an empiric, stepwise, non personalised biomarker informed fashion. A proposed future focus to treating ALK to improve the chronicity of this disease and even promote cure, is to deliver a personalised dynamic approach to care, with rational combinations of drugs in conjunction with local ablative therapies to prevent and constantly proactively alter clonal selection. Such an approach would be informed by precision imaging with MRI-brain and FDG-PETs sequentially, and by regular plasma sampling including for circulating tumour DNA sequencing with personalised therapeutic switches occurring prior to the emergence of radiological and clinical relapse. Such an approach to care will require a complete paradigm shift in the way we approach the treatment of advanced cancer, however evidence to date in ALK+ lung cancers, support this new frontier of investigation.

Jafarzadeh, S., et al. (2022). "Concanavalin A-conjugated gold nanoparticle/silica quantum dot (AuNPs/SiQDs-Con A)-based platform as a fluorescent nanoprobe for the bioimaging of glycan-positive cancer cells." RSC Adv **12**(14): 8492-8501.

The glycan receptor is a glycosylphosphatidylinositol glycoprotein that is overexpressed on the surface of various cancer cells and has been utilized for wide applications. In the present work, the surface of citrate-capped gold nanoparticles (cit-AuNPs) was modified with mercaptopropionic acid (MPA) molecules to provide carboxylic groups for

secondary functionalization with amine anchored-silica quantum dots (Si-NH2 QDs) to produce cit-AuNPs-MPA/Si-NH2 QDs fluorescent nanoparticles. Concanavalin A (Con A) molecules were attached through thiol-AuNP bonds to produce the final cit-AuNPs/MPA/Si-NH2 QDs/Con A smart nanoparticles. The synthesized novel cit-AuNPs/MPA/Si-NH2 QDs/Con A nanoparticles were utilized for the bioimaging of glycan-overexpressed breast cancer cells. Fluorescence microscopy and flow cytometry results revealed that the cit-AuNPs/MPA/Si-NH2 QDs/Con A NPs can be efficiently taken up by cancer cells, with differentiating ability between overexpressed cancer cells and low-expressed normal cells. The cellular viability of the cit-AuNPs/MPA/Si-NH2 QDs/Con A NPs was tested by the MTT test, proving their biocompatible nature at the 200 mug mL(-1) level. In conclusion, the fabricated cit-AuNPs/MPA/Si-NH2 QDs/Con A NPs could be utilized for the bioimaging of MCF-7 cancer cells even in the clinical setting after proper in vivo validation.

Jeon, J., et al. (2020). "Chemiluminescence resonance energy transfer-based nanoparticles for quantum yield-enhanced cancer phototheranostics." Sci Adv **6**(21): eaaz8400.

Chemiluminescence (CL) has recently gained attention for CL resonance energy transfer (CRET)-mediated photodynamic therapy of cancer. However, the short duration of the CL signal and low quantum yield of the photosensitizer have limited its translational applications. Here, we report CRET-based nanoparticles (CRET-NPs) to achieve quantum yield-enhanced cancer phototheranostics by reinterpreting the hidden nature of CRET. Owing to reactive oxygen species (ROS)-responsive CO2 generation, CRET-NPs were capable of generating a strong and long-lasting photoacoustic signal in the tumor tissue via thermal expansion-induced vaporization. In addition, the CRET phenomenon of the NPs enhanced ROS quantum yield of photosensitizer through both electron transfer for an oxygen-independent type I photochemical reaction and self-illumination for an oxygen-dependent type II photochemical reaction. Consequently, owing to their high ROS quantum yield, CRET-NPs effectively inhibited tumor growth with complete tumor growth inhibition in 60% of cases, even with a single treatment.

Jeong, S., et al. (2017). "Cancer-Microenvironment-Sensitive Activatable Quantum Dot Probe in the Second Near-Infrared Window." Nano Lett **17**(3): 1378-1386.

Recent technological advances have expanded fluorescence (FL) imaging into the second near-infrared region (NIR-II; wavelength = 1000-1700 nm), providing high spatial resolution through deep tissues. However, bright and compact fluorophores are rare in this region, and sophisticated control over NIR-II probes has not been fully achieved yet. Herein, we report an enzyme-activatable NIR-II probe that exhibits FL upon matrix metalloprotease activity in tumor microenvironment. Bright and stable PbS/CdS/ZnS core/shell/shell quantum dots (QDs) were synthesized as a model NIR-II fluorophore, and activatable modulators were attached to exploit photoexcited electron transfer (PET) quenching. The quasi type-II QD band alignment allowed rapid and effective FL modulations with the compact surface ligand modulator that contains methylene blue PET quencher. The modulator was optimized to afford full enzyme accessibility and high activation signal surge upon the enzyme activity. Using a colon cancer mouse model, the probe demonstrated selective FL activation at tumor sites with 3-fold signal enhancement in 10 min. Optical phantom experiments confirmed the advantages of the NIR-II probe over conventional dyes in the first near-infrared region.

Ji, M. Y., et al. (2012). "The detection of EBP50 expression using quantum dot immunohistochemistry in pancreatic cancer tissue and down-regulated EBP50 effect on PC-2 cells." J Mol Histol **43**(5): 517-526.

Ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50) is a putative tumor suppressor that is correlated with many human cancers. However, the function of EBP50 in pancreatic cancer (PC) has not been described. In this paper, the EBP50 expression level in PC tissues was characterized. In vitro, the effects of EBP50 down-regulation by siRNA in PC-2 and MiaPaCa-2 cells were evaluated. In addition, possible mechanisms that mediate the influence of EBP50 were examined. Our results show that the EBP50 expression pattern changes during transformation as there is a loss of the normal apical membrane distribution and an ectopic cytoplasmic over-expression of EBP50; furthermore, the EBP50 expression level is subsequently decreased during malignant progression. Down-regulation of EBP50 promoted cancer cell proliferation, increased the colony-forming ability of cells and accelerated the G1-to-S progression. Additionally, the loss of EBP50 accentuated beta-catenin activity, increased cyclin E and phosphorylated Rb expression, and attenuated p27 expression compared to control cells. Our results suggest that EBP50 may function as a potential tumor suppressor.

Jie, G., et al. (2019). "Multifunctional DNA nanocage with CdTe quantum dots for fluorescence detection of human 8-oxoG DNA glycosylase 1 and doxorubicin delivery to cancer cells." Mikrochim Acta **186**(2): 85.

A multifunctional DNA nanocage containing CdTe quantum dots (QDs) was prepared. It was applied to the fluorometric detection of human 8-oxoG DNA glycosylase 1 (hOGG1) by exonuclease-assisted cycling

amplification technique. When loaded with the cancer drug doxorubicin (Dox), the nanocage is also a versatile probe for fluorescence imaging of cancer cells, and drug delivery to them. The presence of hOGG1 leads to the division of DNA HP1 (containing 8-oxo-dG) and formation of DNA fragments 1 and 2. Then, HP2 is added to hybridize with DNA 1 and produced lots of trigger DNA (containing nucleolin aptamer) by Exo III-aided cycling amplification. The DNA nanocage was fabricated by linking the trigger DNA to multiple specific DNA strands, and the fluorescent CdTe QDs were further conjugated to the DNA nanocage for sensitive detection of hOGG1 activity. After Dox is incorporated into the DNA nanocage, the fluorescence of Dox is turned off. Once the DNA nanocage enters the MCF-7 cells, the Dox is released and its fluorescence (measured at excitation/emission wavelengths of 480/560 nm) is turned on. The DNA nanocage containing fluorescent QDs and Dox was successfully applied to the fluorometric detection of hOGG1, fluorescence imaging, and therapy of cancer cells, which has great promise in clinical application and treatment of cancer. Graphical abstract A multifunctional DNA nanocage containing CdTe quantum dots and acting as a signalling probe was prepared. It was applied to fluorometric determination of human 8-oxoG DNA glycosylase 1 using cycling amplification technique. It also enables drug delivery to cancer cells if loaded with doxorubicin.

Jie, G., et al. (2011). "Versatile electrochemiluminescence assays for cancer cells based on dendrimer/CdSe-ZnS-quantum dot nanoclusters." Anal Chem **83**(10): 3873-3880.

In this work, a novel dendrimer/CdSe-ZnS-quantum dot nanocluster (NC) was fabricated and used as an electrochemiluminescence (ECL) probe for versatile assays of cancer cells for the first time. A large number of CdSe-ZnS-quantum dots (QDs) were labeled on the NCs due to the many functional amine groups within the NCs, which could significantly amplify the QD's ECL signal. Capture DNA was specially designed as a high-affinity aptamer to the target cell; a novel ECL biosensor for cancer cells was directly accomplished by using the biobarcode technique to avoid cross-reaction. Moreover, magnetic beads (MBs) for aptamers immobilization were combined with the dendrimer/QD NCs probe for signal-on ECL assay of cancer cells, which greatly simplified the separation procedures and favored for the sensitivity improvement. In particular, a novel cycle-amplifying technique using a DNA device on MBs was further employed in the ECL assay of cancer cells, which greatly improved the sensitivity. To the best of our knowledge, this is the first study that the novel dendrimer/QD NCs probe combined with a DNA device cycle-amplifying technique was employed in the ECL assays of cells. Excellent discrimination against target and control cells is demonstrated, indicating that the ECL assays have great potential to provide a sensitive, selective, cost-effective, and convenient approach for early and accurate detection of cancer cells.

Jie, G., et al. (2014). "A novel quantum dot nanocluster as versatile probe for electrochemiluminescence and electrochemical assays of DNA and cancer cells." Biosens Bioelectron **52**: 69-75.

A novel dendritic quantum dot (QD) nanocluster was constructed and used as versatile electrochemiluminescence (ECL) and electrochemical probe for the detection of DNA and cancer cells. Owing to the many functional groups present in the nanoclusters, a large number of QDs were assembled on the nanoclusters, which could greatly amplify both the ECL and electrochemical signals of QDs. Carbon nanotubes (CNTs)/gold nanoparticles' (NPs) hybrids were used as amplified platform for assembling large numbers of DNA on the electrode, which also improve the bioactivity and stability of the electrode. After the QD-DNA signal probe was recognized with target DNA (t-DNA), the amplified ECL signal for the detection of target DNA was obtained. Furthermore, magnetic nanoparticles were employed for cell aptamers immobilization, the same QD nanocluster-DNA probe was also extended for electrochemical detection of cancer cells using sensitive anodic stripping voltammetry (ASV) method, which simplified the separation procedures and improved the sensitivity. It is anticipated that the assays could provide promising and cost effective approach for the early and accurate detection of DNA and cancer cells.

Jie, G., et al. (2013). "Amplified electrochemiluminescence detection of cancer cells using a new bifunctional quantum dot as signal probe." Biosens Bioelectron **50**: 368-372.

In this work, we prepared a new electrochemiluminescent signal probe using a small bifunctional composite quantum dot (QD) with intense electrochemiluminescence (ECL) and excellent magnetic property, and developed a sensitive ECL biosensor for detection of cancer cells via DNA cyclic amplification technique. The graphene oxide (GO) with unique electrical properties was used as nano-amplified platform to immobilize a large number of capture DNA (c-DNA1). The endonuclease-assisted amplification technique was applied to amplify the ECL signal change induced by target cells. Specifically, the bifunctional composite QDs with excellent magnetic property can be conveniently labeled, separated, and developed the ECL signal probe, thus an ECL method for rapid and sensitive detection of cancer cells was developed. So far, it is for the first time that the small magnetic

electrochemiluminescent QDs were applied to the assays of cancer cells by using amplification strategy, which is expected to have great potential for early clinical diagnosis of cancer.

Jie, G., et al. (2014). "A fluorescent polymeric quantum dot/aptamer superstructure and its application for imaging of cancer cells." Chem Asian J **9**(5): 1261-1264.

In this work, a novel polymeric quantum dot/aptamer superstructure with a highly intense fluorescence was fabricated by a molecular engineering strategy and successfully applied to fluorescence imaging of cancer cells. The polymeric superstructure, which is composed of both multiple cell-based aptamers and a high ratio of quantum dot (QD)-labeled DNA, exploits the target recognition capability of the aptamer, an enhanced cell internalization through multivalent effects, and cellular disruption by the polymeric conjugate. Importantly, the polymeric superstructure exhibits an increasingly enhanced fluorescence with recording time and is thus suitable for long-term fluorescent cellular imaging. The unique and excellent fluorescence property of the QD superstructure paves the way for developing polymeric QD superstructures that hold promise for applications such as in vivo imaging.

Jigyasu, A. K., et al. (2020). "Biological Synthesis of CdTe Quantum Dots and Their Anti-Proliferative Assessment Against Prostate Cancer Cell Line." J Nanosci Nanotechnol **20**(6): 3398-3403.

Quantum dots (QDs) are semiconducting materials which have a wide array of applications starting from semiconducting devices, in humidity and pressure sensors and in medical imaging including cancer therapy. In the present study, cadmium telluride (CdTe) QDs were synthesized by a biological method using yeast cells, Saccharomyces cerevisiae in modified Czapek's medium. QDs were characterized by transmission electron microscopy and X-ray diffraction. Cancer cells were treated with 2, 4, 8 and 16 muM concentrations of CdTe QDs for 24 h. The anti-proliferative activity was determined by using MTT assay, by evaluating the production of reactive oxygen species (ROS), and also by nuclear apoptosis and cell cycle analysis using a flow cytometer against human prostate carcinoma cell line PC-3. The size of the CdTe QDs was approximately 2 nm. In vitro anti-proliferative study showed that CdTe QDs induced cell death and nuclear apoptosis in a dosedependent manner. CdTe QDs induced significant increase in ROS level in PC-3 cells which was dose-dependent. Moreover, CdTe also arrested growth of PC-3 cells in the G2/M phase of the cell cycle. This study elucidates the apoptotic activity of CdTe QDs on prostate carcinoma which could provide useful insights to researchers for its clinical application.

Jin, H., et al. (2019). "Quantum Dot Based Fluorescent Traffic Light Nanoprobe for Specific Imaging of Avidin-Type Biotin Receptor and Differentiation of Cancer Cells." Anal Chem **91**(14): 8958-8965.

Sensitive and specific visualization of cell surface biotin receptors (BRs) a class of clinically important biomarkers, remains a challenge. In this work, a dual-emission ratiometric fluorescent nanoprobe is developed for specific imaging of cell surface avidin, a subtype of BRs. The nanoprobe comprises a dual-emission quantum dot nanohybrid, wherein a silica-encapsulated red-emitting QD (rQD@SiO2) is used as the "core" and green-emitting QDs (gQDs) are used as "satellites", which are further decorated with a new "love-hate"-type BR ligand, a phenanthroline-biotin conjugate with an amino linker. The nanoprobe shows intense rQD emission but quenched gQD emission by the BR ligand. Upon imaging, the rQD emission stays constant and the gQD emission is restored as cell surface avidin accrues. Accordingly, the overlaid fluorescence color collected from red and green emission changes from red to yellow and then to green. We refer to such a color change as a traffic light pattern and the nanoprobe as a fluorescent traffic light nanoprobe. We demonstrate the application of our fluorescent traffic light nanoprobe to characterize cancer cells. By the traffic light pattern, cervical carcinoma and normal cells, as well as different-type cancer cells including BR-negative colon cancer cells, BR-positive hepatoma carcinoma cells, breast cancer cells, and their subtypes, have been visually differentiated. We further demonstrate a use of our nanoprobe to distinguish the G2 phase from other stages in a cell cycle. These applications provide new insights into visualizing cell surface biomarkers with remarkable imaging resolution and accuracy.

Jin, L. H., et al. (2012). "Enhanced detection sensitivity of pegylated CdSe/ZnS quantum dots-based prostate cancer biomarkers by surface plasmon-coupled emission." Biosens Bioelectron **33**(1): 284-287.

We demonstrate the fabrication and detection of quantum dots (QDs)-based prostate specific antigens (PSAs) cancer protein biochips by using enhanced surface plasmon-coupled emission measurements (SPCE). The PSAs are immobilized on a SiO(2)-protected thin gold substrate and pegylated QDs which conjugated with antibodies of PSA are used as fluorescent probes. Due to the excellent brightness of the QDs and the high directionality of emission, as well as the high light collection efficiency of SPCE, the limit of detection (LOD) is down to 10 fg/mL (equal to 0.3 fM) for the PSA chips by using QDs-based cancer protein. We expect that this QDs-based SPCE measurement

system with the low LOD supplies a great potential for detecting various cancer biomarkers that are present in only low concentrations within the human body.

Johari-Ahar, M., et al. (2016). "Methotrexate-conjugated quantum dots: synthesis, characterisation and cytotoxicity in drug resistant cancer cells." J Drug Target **24**(2): 120-133.

Methotrexate (MTX), a folic acid derivative, is a potent anticancer used for treatment of different malignancies, but possible initiation of drug resistance to MTX by cancer cells has limited its applications. Nanoconjugates (NCs) of MTX to quantum dots (QDs) may favour the cellular uptake via folate receptors (FRs)-mediated endocytosis that circumvents the efflux functions of cancer cells. We synthesised MTX-conjugated l-cysteine capped CdSe QDs (MTX-QD nanoconjugates) and evaluated their internalisation and cytotoxicity in the KB cells with/without resistancy to MTX. The NCs were fully characterised by high resolution transmission electron microscopy (HR-TEM), atomic force microscopy (AFM), dynamic light scattering (DLS) and optical spectroscopy. Upon conjugation with MTX, the photoluminescence (PL) properties of QDs altered, while an obvious quenching in PL of QDs was observed after physical mixing. The MTX-QD nanoconjugates efficiently internalised into the cancer cells, and induced markedly high cytotoxicity (IC50, 12.0 microg/mL) in the MTX-resistant KB cells as compared to the free MTX molecules (IC50,105.0 microg/mL), whereas, these values were respectively about 7.0 and 0.6 microg/mL in the MTX-sensitive KB cells. Based on these findings, the MTX-QD nanoconjugates are proposed for the targeted therapy of MTX-resistant cancers, which may provide an improved outcome in the relapsed FR-overexpressing cancers.

Jokerst, J. V., et al. (2009). "Nano-bio-chips for high performance multiplexed protein detection: determinations of cancer biomarkers in serum and saliva using quantum dot bioconjugate labels." Biosens Bioelectron **24**(12): 3622-3629.

The integration of semiconductor nanoparticle quantum dots (QDs) into a modular, microfluidic biosensor for the multiplexed quantitation of three important cancer markers, carcinoembryonic antigen (CEA), cancer antigen 125 (CA125), and Her-2/Neu (C-erbB-2) was achieved. The functionality of the integrated sample processing, analyte capture and detection modalities was demonstrated using both serum and whole saliva specimens. Here, nano-bio-chips that employed a fluorescence transduction signal with QD-labeled detecting antibody were used in combination with antigen capture by a microporous agarose bead array supported within a microfluidics ensemble so as to complete the sandwich-type immunoassay. The utilization of QD probes in this miniaturized biosensor format resulted in signal amplification 30 times relative to that of standard molecular fluorophores as well as affording a reduction in observed limits of detection by nearly 2 orders of magnitude (0.02 ng/mL CEA; 0.11 pM CEA) relative to enzyme-linked immunosorbent assay (ELISA). Assay validation studies indicate that measurements by the nano-bio-chip system correlate to standard methods at R(2)=0.94 and R(2)=0.95 for saliva and serum, respectively. This integrated nano-bio-chip assay system, in tandem with next-generation fluorophores, promises to be a sensitive, multiplexed tool for important diagnostic and prognostic applications.

Jose, A., et al. (2018). "Multifunctional fluorescent iron quantum clusters for non-invasive radiofrequency ablationof cancer cells." Colloids Surf B Biointerfaces **165**: 371-380.

This work reports the potential of iron quantum clusters (FeQCs) as a hyperthermia agent for cancer, by testing its in-vitro response to shortwave (MHz range), radiofrequency (RF) waves non-invasively. Stable, fluorescent FeQCs of size approximately 1nm prepared by facile aqueous chemistry from endogenous protein haemoglobin were found to give a high thermal response, with a DeltaT approximately 50 degrees C at concentrationsas low as165mug/mL. The as-prepared nanoclusters purified by lyophilization as well as dialysis showed a concentration, power and time-dependent RF response, with the lyophilized FeQCs exhibiting pronounced heating effects. FeQCs were found to be cytocompatible to NIH-3T3 fibroblast and 4T1 cancer cells treated at concentrations upto 1000mug/mL for 24h. Upon incubation with FeQCs and exposure to RF waves, significant cancer cell death was observed which proves its therapeutic ability. The fluorescent ability of the clusters could additionally be utilized for imaging cancer cells upon excitation at approximately 450nm. Further, to demonstrate the feasibility of imparting additional functionality such as drug/biomolecule/dye loading to FeQCs, they were self assembled with cationic polymers to form nanoparticles. Self assembly did not alter the RF heating potential of FeQCs and additionally enhanced its fluorescence. The multifunctional fluorescent FeQCs therefore show good promise as a novel therapeutic agent for RF hyperthermia and drug loading.

Ju, Y. Y., et al. (2022). "Atomically Precise Water-Soluble Graphene Quantum Dot for Cancer Sonodynamic Therapy." Adv Sci (Weinh) **9**(19): e2105034.

Although water-soluble graphene quantum dots (GQDs) have shown various promising bio-applications due to their intriguing optical and chemical

properties, the large heterogeneity in compositions, sizes, and shapes of these GQDs hampers the better understanding of their structure-properties correlation and further uses in terms of large-scale manufacturing practices and safety concerns. It is shown here that a water-soluble atomically-precise GQD (WAGQD-C96) is synthesized and exhibits a deep-red emission and excellent sonodynamic sensitization. By decorating sterically hindered water-soluble functional groups, WAGQD-C96 can be monodispersed in water without further aggregation. The deep-red emission of WAGQD-C96 facilitates the tracking of its bio-process, showing a good cell-uptake and long-time retention in tumor tissue. Compared to traditional molecular sonosensitizers, WAGQD-C96 generates superior reactive oxygen species and demonstrates excellent tumor inhibition potency as an anti-cancer sonosensitizer in in vivo studies. A good biosafety of WAGQD-C96 is validated in both in vitro and in vivo assays.

Jung, K. H., et al. (2011). "99mTc-Hydrazinonicotinamide epidermal growth factor-polyethylene glycol-quantum dot imaging allows quantification of breast cancer epidermal growth factor receptor expression and monitors receptor downregulation in response to cetuximab therapy." J Nucl Med **52**(9): 1457-1464.

UNLABELLED: Therapy of cancer, including basallike breast tumors, that targets the epidermal growth factor receptor (EGFR) would greatly benefit from noninvasive methods that can quantitatively monitor receptor status and treatment response. METHODS: Here, we investigated the potential of a novel technique based on streptavidin cadmium selenide/zinc sulfide quantum dots (Qdots) multiplexed with polyethylene glycol (PEG), epidermal growth factor (EGF), and (99m)Tc-hydrazinonicotinamide. In vitro binding affinity and specificity were evaluated in cultured cells. Biodistribution studies and in vivo imaging were performed in murine breast tumor xenografts of basallike phenotype MDA-MB-468 cells and EGFR-negative cells. RESULTS: (99m)Tc-hydrazinonicotinamide EGF-PEG-Qdot showed specific and high-affinity EGFR targeting on confocal microscopy, immunoblotting, and binding assays. When intravenously injected, MDA-MB-468 tumors were visualized with high contrast by both optical and scintigraphic imaging. Scintigraphic image-based quantification correctly discriminated high-EGFR-expressing MDA-MB-468 tumors from other tumors, and image-based tumor uptake closely correlated to EGFR content. Importantly, serial imaging of MDA-MB-468 tumors responding to cetuximab therapy could detect a significant reduction of tumor uptake that was paralleled by downregulation of EGFR expression. Furthermore, high baseline uptake predicted good response to cetuximab therapy. CONCLUSION: (99m)Tc-hydrazinonicotinamide EGF-PEG-Qdot provides EGFR-targeted imaging of breast tumors and may allow noninvasive monitoring of EGFR status in living subjects before and after targeted therapies.

Juzenas, P., et al. (2008). "Quantum dots and nanoparticles for photodynamic and radiation therapies of cancer." Adv Drug Deliv Rev **60**(15): 1600-1614.

Semiconductor quantum dots and nanoparticles composed of metals, lipids or polymers have emerged with promising applications for early detection and therapy of cancer. Quantum dots with unique optical properties are commonly composed of cadmium contained semiconductors. Cadmium is potentially hazardous, and toxicity of such quantum dots to living cells, and humans, is not yet systematically investigated. Therefore, search for less toxic materials with similar targeting and optical properties is of further interest. Whereas, the investigation of luminescence nanoparticles as light sources for cancer therapy is very interesting. Despite advances in neurosurgery and radiotherapy the prognosis for patients with malignant gliomas has changed little for the last decades. Cancer treatment requires high accuracy in delivering ionizing radiation to reduce toxicity to surrounding tissues. Recently some research has been focused in developing photosensitizing quantum dots for production of radicals upon absorption of visible light. In spite of the fact that visible light is safe, this approach is suitable to treat only superficial tumours. Ionizing radiation (X-rays and gamma rays) penetrate much deeper thus offering a big advantage in treating patients with tumours in internal organs. Such concept of using quantum dots and nanoparticles to yield electrons and radicals in photodynamic and radiation therapies as well their combination is reviewed in this article.

Kadian, S., et al. (2020). "Targeted bioimaging and sensing of folate receptor-positive cancer cells using folic acid-conjugated sulfur-doped graphene quantum dots." Mikrochim Acta **187**(8): 458.

For the first time is reported a facile in situ synthesis of folic acid-conjugated sulfur-doped graphene quantum dots (FA-SGQDs) through simple pyrolysis of citric acid (CA), 3-mercaptopropionic acid (MPA), and FA. The as-prepared FA-SGQDs were extensively characterized to confirm the synthesis and incidence of FA molecule on the surface of SGQDs through advanced characterization techniques. Upon excitation at 370-nm wavelength, FA-SGQDs exhibited blue fluorescence with an emission band at 455 nm. While exhibiting relatively high quantum yield (~ 78%), favorable biocompatibility, excellent photostability, and desirable optical properties, the FA-SGQDs showed

suitability as a fluorescent nanoprobe to distinguish the folate receptor (FR)-positive and FR-negative cancer cells. The experimental studies revealed that FA-SGQDs aptly entered into FR-positive cancer cells via a non-immunogenic FR-mediated endocytosis process. Additionally, the FA-SGQDs exhibited excellent free radical scavenging activity. Hence, these FA-SGQDs hold high promise to serve as efficient fluorescent nanoprobes for the pre-diagnosis of cancer through targeted bioimaging and other pertinent biological studies. Graphical abstract.

Kalaiyarasan, G., et al. (2019). "Amygdalin-Functionalized Carbon Quantum Dots for Probing beta-Glucosidase Activity for Cancer Diagnosis and Therapeutics." ACS Biomater Sci Eng **5**(6): 3089-3099.

A fluorescence active nanosystem capable of targeting specific receptors of cancer cells with or without a biorecognition element is advantageous for biosensor studies. Herein, a naturally occurring anticancer drug, amygdalin (synthetic form: Laetrile, a misnomer: vitamin B17), has been modified on the surface of carbon quantum dots, prepared by a hydrothermal method, to probe beta-glucosidase activity. Despite its cyanide toxicity, amygdalin is recently revived to be an anticancer molecule, and the risk factor can be optimized by understanding its binding efficiency with beta-glucosidase in the cancer cells. In this study, an in vitro biorecognition pattern of amygdalin-functionalized carbon quantum dots (Amy@CQDs) toward beta-glucosidase is typically evaluated by an aggregation-induced fluorescence emission mechanism. The optical functionality and structural integrity of CQDs before and after functionalization with amygdalin are comprehensively studied by spectroscopic and microscopic techniques. Our results demonstrate that Amy@CQDs is a stable hydrophilic graphitic carbon nanostructure exhibiting selective fluorescence quenching upon interaction with beta-glucosidase, enabling the lowest detection limit of 134 nM. Hydrolysis products of amygdalin mediated by beta-glucosidase were further confirmed by HPLC and colorimetric methods, indicating the selective binding of the prepared Amy@CQDs, which may find a useful application in cancer diagnosis and therapeutics.

Kalkal, A., et al. (2020). "Biofunctionalized Graphene Quantum Dots Based Fluorescent Biosensor toward Efficient Detection of Small Cell Lung Cancer." ACS Appl Bio Mater **3**(8): 4922-4932.

Quantitative detection of cancer biomarkers with higher accuracy and sensitivity provides an effective platform for screening, monitoring, early diagnosis, and disease surveillance. The present work demonstrates the fabrication and application of fluorescent turn-on biosensor for ultrasensitive detection of small cell lung cancer biomarker utilizing biofunctionalized graphene quantum dots as the energy donor and gold nanoparticles (AuNPs) as the energy acceptor. One-pot and the bottom-up hydrothermal route have been employed for the synthesis of in situ amine-functionalized and nitrogen-doped graphene quantum dots (amine-N-GQDs) and further characterized experimentally by different analytical techniques. The molecular simulation studies were performed using the Material Studio software for optimizing the possible chemical structure of synthesized amine-N-GQDs, a comprehensive analysis of experimental results to validate the presence of potential N-doping and amine functionalization sites. Then monoclonal neuron-specific enolase antibodies (anti-NSE) were covalently immobilized to amine-N-GQDs to provide the biofunctionalized GQDs (anti-NSE/amine-N-GQDs). A label-free and efficient fluorescent biosensor based on nanosurface energy transfer (NSET) between anti-NSE/amine-N-GQDs and AuNPs has been developed for neuron-specific enolase (NSE) detection. The fluorescence response studies of anti-NSE/amine-N-GQDs@AuNPs nanoprobe conducted as a function of NSE antigen exhibited fast response time (16 min), broader linear detection range (0.1 pg mL(-1) to 1000 ng mL(-1)), and remarkably low detection limit (0.09 pg mL(-1)). Additionally, the fluorescent biosensor exhibited excellent performance in real samples, with an average recovery value of 94.69%.

Kaul, Z., et al. (2007). "Quantum dot-based mortalin staining as a visual assay for detection of induced senescence in cancer cells." Ann N Y Acad Sci **1100**: 368-372.

Quantum dots (QDs) are fluorescent nanocrystals that are emerging as fine alternatives to the conventional organic dyes. They have several advantages including greater photostability and a wider range of excitation-emission wavelengths. By using mortalin staining as a model, we initially demonstrated that the QDs are more stable and provide better resolution in protein imaging in fixed cells. With the help of an internalizing antibody, we generated internalizing QD (i-QD) and demonstrated its inertness to cell replication, structure, and viability. Based on the superior resolution, stability and inertness, we propose the use of QD staining of mortalin as a cell-based visual assay to screen for senescence-inducing drugs, proteins, and siRNAs.

Kaul, Z., et al. (2003). "Mortalin imaging in normal and cancer cells with quantum dot immuno-conjugates." Cell Res **13**(6): 503-507.

Quantum dots are the nanoparticles that are recently emerging as an alternative to organic fluorescence probes in cell biology and biomedicine,

and have several predictive advantages. These include their i) broad absorption spectra allowing visualization with single light source, ii) exceptional photo-stability allowing long term studies and iii) narrow and symmetrical emission spectrum that is controlled by their size and material composition. These unique properties allow simultaneous excitation of different size of quantum dots with a single excitation light source, their simultaneous resolution and visualization as different colors. At present there are only a few studies that have tested quantum dots in cellular imaging. We describe here the use of quantum dots in mortalin imaging of normal and cancer cells. Mortalin staining pattern with quantum dots in both normal and cancer cells mimicked those obtained with organic florescence probes and were considerably stable.

Kaur, H. (2019). "Aptamer Conjugated Quantum Dots for Imaging Cellular Uptake in Cancer Cells." J Nanosci Nanotechnol **19**(7): 3798-3803.

The fluorescence labeling of aptamers is a useful technology for aptamer tracking and imaging on the cells. The aptamer SL(2)-B, against the heparin binding domain (HBD) of VEGF165 protein, was linked to QDs, producing the QD-SL(2)-B aptamer conjugate. The QDs and the QD-aptamer conjugate were characterized and photobleaching effect was studied prior to the cellular incubation. Fluorescence imaging showed that the QD-SL(2)-B aptamer conjugate could specifically recognize Hep G2 liver cancer cells and is taken up by the cells without addition of any external transfecting or cell permeabilizing agent. In addition, the results also indicate that incubation time is important for the aptamer cellular uptake and to exhibit its antiproliferative activity on Hep G2 liver cancer cells. This QDs labeling technique provides a new strategy for labeling aptamer molecules for aptamer detection, imaging and understanding their cellular uptake.

Khan, F. A., et al. (2020). "Quantum dots encapsulated with curcumin inhibit the growth of colon cancer, breast cancer and bacterial cells." Nanomedicine (Lond) **15**(10): 969-980.

Aim: To synthesize and examine the impact of free Eudragit((R)) RS 100 nanoparticles (LN01), Quantum dots curcumin-loaded Eudragit RS 100 nanoparticles (LN04), and un-encapsulated curcumin nanoparticles (LN06) on cancerous and bacterial cells. Materials & methods: The LN01, LN04, LN06 were synthesized and characterized by Fourier transform infrared, zeta potential, UV-Vis spectroscopy, transmission electron microscopy and scanning electron microscopy and their biological activities were evaluated. Results: LN04 profoundly inhibited the growth of colon (HCT-116) cancerous cells (10.64% cell viability) and breast cancer (MCF-7) cells (10.32% cell viability) with compared to LN01 and LN06. Normal cells (HEK-293) did not show any inhibition after treatments. In addition, LN04 show better inhibitory action on bacterial growth compared with LN01 and LN06. Conclusion: We suggest that LN04 selectively target cancerous and bacterial cells and therefore possess potential anticancer and antibacterial capabilities.

Ki, J., et al. (2017). "High-content cell death imaging using quantum dot-based TIRF microscopy for the determination of anticancer activity against breast cancer stem cell." J Biophotonics **10**(1): 118-127.

We report a two color monitoring of drug-induced cell deaths using total internal reflection fluorescence (TIRF) as a novel method to determine anticancer activity. Instead of cancer cells, breast cancer stem cells (CSCs) were directly tested in the present assay to determine the effective concentration (EC50) values of camptothecin and cisplatin. Phosphatidylserine and HMGB1 protein were concurrently detected to observe apoptotic and necrotic cell death induced by anticancer drugs using quantum dot (Qdot)-antibody conjugates. Only 50-to-100 breast CSCs were consumed at each cell chamber due to the high sensitivity of Qdot-based TIRF. The high sensitivity of Qdot-based TIRF, that enables the consumption of a small number of cells, is advantageous for cost-effective large-scale drug screening. In addition, unlike MTT assay, this approach can provide a more uniform range of EC50 values because the average values of single breast CSCs fluorescence intensities are observed to acquire EC50 values as a function of dose. This research successfully demonstrated the possibility that Qdot-based TIRF can be widely used as an improved alternative to MTT assay for the determination of anticancer drug efficacies.

Kim, J. H., et al. (2017). "Anticancer luminescent gold quantum clusters for in situ cancer-selective marking-imaging-targeting." Nanoscale **9**(26): 9071-9082.

Ultrafine Au quantum clusters (QCs) were synthesized by etching host Au nanoparticles in the presence of ethylenediamine (en) and exhibited both strong photoluminescence (PL) and specific anticancer activity. The cutting-edge feature of this QC compound comprises subnanometer-size rhombohedral Au8, which consists of 8 units of the anticancer motif, namely, an Au(+)(en) complex (Au(en)QCs), which contributes to photo- and physicochemical stability as well as subcellular theranostic activity in intracellular PL imaging and in situ targeting. Moreover, the Au(en)QCs can be surface-encapsulated by transferrins (Tf) to create TfAu(en)QCs as a multipurpose drug carrier owing to numerous merits, which include cancer-selective biolabeling, high loading/release efficiency,

high activity against drug-resistant tumor cells, low toxicity to normal cells, and physiological stability against biothiols, e.g., glutathiones. These versatile features, which are due to intrinsic optical and anticancer properties, provide potential as a single-drug delivery PL probe for preclinical applications, which has yet to be achieved using conventional nanoclusters.

Kim, M., et al. (2022). "Detection of ovarian cancer via the spectral fingerprinting of quantum-defect-modified carbon nanotubes in serum by machine learning." Nat Biomed Eng **6**(3): 267-275.

Serum biomarkers are often insufficiently sensitive or specific to facilitate cancer screening or diagnostic testing. In ovarian cancer, the few established serum biomarkers are highly specific, yet insufficiently sensitive to detect early-stage disease and to impact the mortality rates of patients with this cancer. Here we show that a 'disease fingerprint' acquired via machine learning from the spectra of near-infrared fluorescence emissions of an array of carbon nanotubes functionalized with quantum defects detects high-grade serous ovarian carcinoma in serum samples from symptomatic individuals with 87% sensitivity at 98% specificity (compared with 84% sensitivity at 98% specificity for the current best clinical screening test, which uses measurements of cancer antigen 125 and transvaginal ultrasonography). We used 269 serum samples to train and validate several machine-learning classifiers for the discrimination of patients with ovarian cancer from those with other diseases and from healthy individuals. The predictive values of the best classifier could not be attained via known protein biomarkers, suggesting that the array of nanotube sensors responds to unidentified serum biomarkers.

Kim, M. W., et al. (2017). "Cancer-targeted Nucleic Acid Delivery and Quantum Dot Imaging Using EGF Receptor Aptamer-conjugated Lipid Nanoparticles." Sci Rep **7**(1): 9474.

Co-application of fluorescent quantum dot nanocrystals and therapeutics has recently become a promising theranostic methodology for cancer treatment. We developed a tumor-targeted lipid nanocarrier that demonstrates notable efficacy in gene delivery as well as tumor bio-imaging. Coupling of aptamer molecules against the EGF receptor (EGFR) to the distal termini of lipid nanoparticles provided the carrier with tumor-specific recognition capability. The cationic lipid component, referred to as O,O'-dimyristyl-N-lysyl glutamate (DMKE), was able to effectively complex with anionic small-interfering RNA (siRNA). The hydrophobic quantum dots (Q-dots) were effectively incorporated in hydrophobic lipid bilayers at an appropriate Q-dot to lipid ratio. In this study, we optimized the liposomal formula of aptamer-conjugated liposomes containing Q-dots and siRNA molecules (Apt-QLs). The anti-EGFR Apt-QLs exhibited remarkable EGFR-dependent siRNA delivery as well as fluorescence imaging, which were analyzed in cultured cancer cells and tumor xenografts in mice. These results imply that the formulation of Apt-QLs could be widely utilized as a carrier for tumor-directed gene delivery and bio-imaging.

Kim, M. W., et al. (2019). "Anti-EGF Receptor Aptamer-Guided Co-Delivery of Anti-Cancer siRNAs and Quantum Dots for Theranostics of Triple-Negative Breast Cancer." Theranostics **9**(3): 837-852.

Many aptamers have been evaluated for their ability as drug delivery vehicles to target ligands, and a variety of small interfering RNAs (siRNAs) have been tested for their anti-cancer properties. However, since these two types of molecules have similar physicochemical properties, it has so far been difficult to formulate siRNA-encapsulating carriers guided by aptamers. Here, we propose aptamer-coupled lipid nanocarriers encapsulating quantum dots (QDs) and siRNAs for theragnosis of triple-negative breast cancer (TNBC). Methods: Hydrophobic QDs were effectively incorporated into lipid bilayers, and then therapeutic siRNAs were complexed with QD-lipid nanocarriers (QLs). Finally, anti-EGFR aptamer-lipid conjugates were inserted into the QLs for TNBC targeting (aptamo-QLs). TNBC-targeting aptamo-QLs were directly compared to anti-EGFR antibody-coupled immuno-QLs. The in vitro delivery of therapeutic siRNAs and QDs to target cells was assessed by flow cytometry and confocal microscopy. The in vivo targeting of siRNAs to tumors and their therapeutic efficacy were evaluated in mice carrying MDA-MB-231 tumors. Results: Both types of EGFR-targeting QLs showed enhanced delivery to target cancer cells, resulting in more effective gene silencing and enhanced tumor imaging compared to non-targeting control QLs. Moreover, combinatorial therapy with Bcl-2 and PKC-iota siRNAs loaded into the anti-EGFR QLs was remarkably effective in inhibiting tumor growth and metastasis. Conclusion: In general, the aptamo-QLs showed competitive in vivo delivery and therapeutic efficacy compared to immuno-QLs under the same experimental conditions. Our results show that the anti-EGFR aptamer-guided lipid carriers may be a potential theranostic delivery vehicle for RNA interference and fluorescence imaging of TNBCs.

Ko, N. R., et al. (2020). "Dual pH- and GSH-Responsive Degradable PEGylated Graphene Quantum Dot-Based Nanoparticles for Enhanced HER2-Positive Breast Cancer Therapy." Nanomaterials (Basel) **10**(1).

Dual stimuli-responsive degradable carbon-based nanoparticles (DS-CNPs) conjugated with

Herceptin (HER) and polyethylene glycol (PEG) have been designed for the treatment of HER2-positive breast cancer. Each component has been linked through disulfide linkages that are sensitive to glutathione in a cancer microenvironment. beta-cyclodextrin (beta-CD) on the surface of DS-CNPs formed an inclusion complex (DL-CNPs) with doxorubicin (DOX) at a high loading capacity of 5.3 +/- 0.4%. In response to a high level of glutathione (GSH) and low pH in a tumor environment, DL-CNPs were rapidly degraded and released DOX in a controlled manner via disruption of host-guest inclusion. These novel DL-CNPs exhibited high cellular uptake with low toxicity, which induced the efficient inhibition of antitumor activity both in vitro and in vivo. Cell viability, confocal laser scanning microscopy, and animal studies indicate that DL-CNPs are a great platform with a synergistically enhanced antitumor effect from the dual delivery of HER and DOX in DL-CNPs.

Kobayashi, H., et al. (2009). "Multicolor imaging of lymphatic function with two nanomaterials: quantum dot-labeled cancer cells and dendrimer-based optical agents." Nanomedicine (Lond) **4**(4): 411-419.

AIM: The lymphatics, critical conduits of metastases, are difficult to study because of their size and location. Two approaches to lymphatic imaging have been employed; cancer cell labeling provides information on cell migration and metastasis and macromolecular contrast agents enable visualization of the lymphatic drainage and identification of sentinel lymph node. Only one of these approaches is typically employed during an imaging examination. Here, we demonstrate the combined use of both approaches. METHOD: In this study, we simultaneously visualize migration of quantum dot-labeled melanoma cells and the lymphatics using optically labeled dendrimers in vivo. RESULTS: The appropriate use of two nanomaterials, quantum dots and dendrimers, enabled the simultaneous tracking of cancer cells within draining lymphatics. CONCLUSION: This technique could enable better understanding of lymph node metastasis.

Kobir, M. E., et al. (2022). "Anti-lung cancer drug discovery approaches by polysaccharides: an in silico study, quantum calculation and molecular dynamics study." J Biomol Struct Dyn: 1-17.

Lung cancer (LC) is one of the major and risky health defects even the serious cause for death in concurrent era. But no potential drugs even chemotherapeutic agents have been discovered with approval of health safety although some non-toxic biological macromolecules, such as polysaccharides and polysaccharide-protein complexes, have obtained as anti-lung cancer properties. This study conveys the anti-lung cancer properties of 45 polysaccharide derivatives collected from PubChem database. Primarily, the PASS prediction was performed to depict their anti-cancer activity, and 37 compounds showed the desired results. Next, the chemical descriptors, such as HOMO, LUMO, softness, and hardness etc, were calculated through the density functional theory (DFT) for quantum properties. Secondly, the auto molecular docking was executed to delineate the protein-ligand interactions, binding ability and inhibition of active sites of proteins. Additionally, the compounds showed docking score more than -6.40 kcal/mol, and the highest binding affinity was at -10.00 kcal/mol even 15 compounds have higher binding score (-8.6 to -10.0) than approved drugs, Gemcitabine. Succeeding, the most common protein residue, VAL 647, was blocked by ligands for the main protein (1X2J). In addition, five protein's active sites were determined to make the relative study of protein-ligand interactions. As a result, the target docking against five proteins was performed, and it was found that the targeted docking score as the binding affinity is lower than auto docking. Finally, a comparative study between auto docking and targeted docking was performed for the most common five lung cancer proteins founded in three organisms.

Komoto, Y., et al. (2020). "Detection of an alcohol-associated cancer marker by single-molecule quantum sequencing." Chem Commun (Camb) **56**(91): 14299-14302.

Alcoholic beverages are a well-known risk factor for cancer. N(2)-Ethyl-2'-deoxyguanosine (N(2)-Et-dG) is a promising biomarker for alcohol-associated cancers. However, the lack of a convenient detection method for N(2)-Et-dG hinders the development of practical DNA damage markers. Herein, we develop a detection method for N(2)-Et-dG using a single-molecule quantum sequencing (SMQS) method and machine learning analysis. Our method succeeded in discriminating between N(2)-Et-dG and dG with an accuracy of 99%, using 20 signals. Our developed method quantified the mixing ratio of N(2)-Et-dG from a mixed solution of N(2)-Et-dG and dG. It is shown that our method has the potential to facilitate the development of DNA damage markers, and thus the early detection and prevention of cancers.

Kuepper, C., et al. (2018). "Quantum Cascade Laser-Based Infrared Microscopy for Label-Free and Automated Cancer Classification in Tissue Sections." Sci Rep **8**(1): 7717.

A feasibility study using a quantum cascade laser-based infrared microscope for the rapid and label-free classification of colorectal cancer tissues is presented. Infrared imaging is a reliable, robust, automated, and operator-independent tissue classification method that has been used for differential classification of tissue thin sections identifying

tumorous regions. However, long acquisition time by the so far used FT-IR-based microscopes hampered the clinical translation of this technique. Here, the used quantum cascade laser-based microscope provides now infrared images for precise tissue classification within few minutes. We analyzed 110 patients with UICC-Stage II and III colorectal cancer, showing 96% sensitivity and 100% specificity of this label-free method as compared to histopathology, the gold standard in routine clinical diagnostics. The main hurdle for the clinical translation of IR-Imaging is overcome now by the short acquisition time for high quality diagnostic images, which is in the same time range as frozen sections by pathologists.

Kulkarni, N. S., et al. (2019). "Tyrosine kinase inhibitor conjugated quantum dots for non-small cell lung cancer (NSCLC) treatment." Eur J Pharm Sci **133**: 145-159.

Non-small cell lung cancer is a major sub-type of lung cancer that is associated with a poor diagnosis resulting in poor therapy for the disorder. In order to achieve a better prognosis, innovative multi-functional systems need to be developed which will aide in diagnosis as well as therapy for the disorder. One such multi-functional delivery system fabricated is Quantum Dots (QDs). QDs are photo-luminescent inorganic nanoparticles utilized for tumor detection, preclinically. Erlotinib hydrochloride, a tyrosine kinase inhibitor, is a first-generation drug developed to treat NSCLC. Its active metabolite, Desmethyl Erlotinib (OSI-420), exhibits similar anticancer activity as erlotinib. OSI-420 was conjugated to QDs to fabricate a delivery system and was then characterized by FT-IR, H NMR, UV-VIS, particle size, zeta potential, fluorescence spectroscopy and TEM. Drug loading was estimated using UV-VIS spectroscopy (52.2+/-7.5%). A concentration-dependent release of OSI-420 was achieved using esterase enzymes, which was further confirmed using LC-MS. A cellular uptake study revealed the internalization potential of QDs and QD-OSI 420. A cellular recovery study was performed to confirm the internalization potential. Cell viability studies revealed that QD-OSI 420 conjugates had significantly better efficacy than pure drugs in all tested cell lines. QD conjugated OSI-420 demonstrated an IC60 of 2.5muM in erlotinib-resistant A549 cell lines, where erlotinib or OSI-420 alone could not exhibit 60% inhibition when evaluated up to 20muM. Similar cytotoxic enhancement of erlotinib was seen with QD-OSI 420 in other NSCLC cell lines as well. These results were strengthened by 3D-SCC model of A549 which revealed that QD-OSI 420 was significantly better in reducing in-vitro 3D tumor volume, as compared to pure drugs. This study, being one of its kind, explores the feasibility of conjugating OSI-420 with QDs as an alternative to traditional anti-cancer therapy, by improving intracellular drug delivery.

Kumawat, M. K., et al. (2019). "Preparation of graphene oxide-graphene quantum dots hybrid and its application in cancer theranostics." Mater Sci Eng C Mater Biol Appl **103**: 109774.

Currently, an enormous amount of cancer research based on two-dimensional nano-graphene oxide (GO), as well as zero-dimensional graphene quantum dots (GQDs), is being carried out in the fields of therapeutics and diagnostics. However, the exploration of their hybrid "functional" nanomaterials in the theranostic system is still rare. In the current study, a stable complex of GO and GQDs was formed by an electrostatic layer-by-layer assembly via a polyethylene imine bridge (GO-PEI-GQDs). Furthermore, we compared separate mono-equivalents of the GO-PEI-GQDs complex - GO and GQDs, in terms of cell imaging (diagnostics), photothermal, and oxidative stress response in breast cancer cells (MDA-MB-231). GO-PEI-GQDs showed an excellent photothermal response (44-49 degrees C) upon 808nm laser (0.5Wcm(-2)) exposure for 5min at a concentration up to 50mug/mL. We report new synergistic properties of GO-PEI-GQDs such as stable fluorescence imaging and enhanced photothermal and cytotoxic activities on cancer cells. Composite materials made up of GO and GQDs combining diverse properties help to study 2D-0D heterosystems and improve specific therapeutic systems in theranostics.

Kuntip, N., et al. (2021). "Modeling the Adsorption of the miR-29a Cancer Biomarker on a Graphene Quantum Dot." ACS Omega **6**(33): 21764-21772.

MicroRNAs (miRNAs) are small noncoding RNA molecules associated with the regulation of gene expression in organisms. MiRNAs are focused on as potential cancer biomarkers due to their involvement in cancer development. New potential techniques for miRNA detection are rapidly developed, while there is a lack of effective extraction approaches, especially for miRNAs. Recently, graphene quantum dots (GQDs) have been involved in many disease biosensor platforms including miRNA detection, but no application in miRNA extraction is studied. To extract miRNAs, miRNA adsorption and desorption on GQDs are the key. Thus, in this work, the adsorption mechanism of miRNA on GQDs in solution is revealed using molecular dynamics simulations. The aim is to explore the possibility of using GQDs for miRNA extraction. The folded miR-29a molecule, one of the key cancer biomarkers, is used as a miRNA model. Two systems with one (1miR) and four (4miR) chains of miR-29a were set. MiR-29a molecules in all systems are simultaneously adsorbed on the GQD surface. Our

finding highlights the ability of the GQD in collecting miRNAs in solution. In 1miR, the whole miR-29a chain sits on the GQD face, whereas all miR-29a molecules in 4miR show the "clamping" conformation. No "lying flat" orientation of miR-29a is observed due to the existence of the preserved hairpin region. Interestingly, the 5' end shows tighter binding than the 3' terminus. A design of complementary DNA with the recognition segment involving the sequences close to the 3' end can promote effective miR-29a desorption.

Kuntip, N., et al. (2021). "What Happens When a Complementary DNA Meets miR-29a Cancer Biomarker in Complex with a Graphene Quantum Dot." ACS Appl Bio Mater **4**(12): 8368-8376.

MicroRNAs (miRNAs), short single-stranded noncoding RNA molecules, serve as potential cancer biomarkers due to their involvement in cancer development. One of the strategies to extract miRNAs is to perform the miRNA adsorption on nanomaterials and dissociation by a complementary DNA strand (DNA probe). Recently, graphene quantum dots (GQDs) were found to show a good ability to absorb miRNAs. Thus, in this work, the mechanism of the GQD-adhered miRNA capture by its complementary DNA is revealed using molecular dynamics simulations. miR-29a, a potential cancer biomarker, is used as a miRNA model. Three systems containing one and four chains of miR-29a in addition to one and four complementary DNA probes (1R1D, 1R4D, and 4R4D) were studied. GQDs are the prime targets of a DNA attack. The full coverage of GQDs is required to protect the adsorption of DNA probes on the GQD face. The nucleobase-backbone interactions are the main contributors to miR-DNA interactions in this work. The interbase paring becomes small because most nucleobases of miR-29a and their probe are stacked to maintain their secondary structures, and some are absorbed on the GQD surface. Apparently, weakening of the nucleobase-GQD pi-pi stacking and the intrabase-pairing strength is needed for extracting miR-29a by a probe. Although no GQD-absorbed miR-29a desorption is found here, the basic principles obtained can be useful for further utilization of GQDs and their derivatives for miRNA extraction and detection.

Kurniawan, D., et al. (2021). "Microplasma-Tunable Graphene Quantum Dots for Ultrasensitive and Selective Detection of Cancer and Neurotransmitter Biomarkers." ACS Appl Mater Interfaces **13**(29): 34572-34583.

The effective and precise detection of cancer and neurotransmitter biomarkers including folic acid (FA), dopamine (DA), and epinephrine (EP) are essential for early detection and diagnosis of cancer and neurological disorders and for the development of new drugs. However, it remains challenging to detect FA, DA, and EP with high selectivity and sensitivity with a single material. Herein, we report a photoluminescence (PL)-based selective sensing of FA, DA, and EP with nitrogen-doped graphene quantum dots (NGQDs) synthesized from biocompatible chitosan under ambient conditions using atmospheric pressure microplasmas. By regulating the pH, the selective detection is achieved in broad ranges from 0.8 to 80 muM for FA and 0.4 to 100 muM for both DA and EP with the very low limits of detections of 81.7, 57.8, and 16.7 nM for FA, DA, and EP, respectively. The developed PL sensing method shows the high throughput of 5000 detections per hour. Moreover, highly stable colloidal NGQD dispersion with 100 mug/mL concentration for at least 100 PL detections is produced in 1 h by a single microplasma, and the process is scalable. The mechanisms of the outstanding performance are related to the enhanced, size-dependent pi-pi stacking attraction between the NGQDs and the pH-regulated chemical states of the analytes and the associated pH-specific photo-induced electron transfer and PL.

Kwon, H., et al. (2013). "In vitro and in vivo imaging of prostate cancer angiogenesis using anti-vascular endothelial growth factor receptor 2 antibody-conjugated quantum dot." Korean J Radiol **14**(1): 30-37.

OBJECTIVE: Authors aimed to determine the targeting ability of vascular endothelial growth factor receptor 2 (VEGFR2)-conjugated quantum dots (QDs) in vitro, and apply it for a xenograft prostate cancer mouse model. MATERIALS AND METHODS: Conjugation reaction of QDs was performed by using the N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) and sulfo-(N-hydroxysulfosuccinimide) (Sulfo-NHS). The human umbilical vein cord endothelial cells (HUVECs) were incubated with QDs, conjugated with antiVGFR2, to see a specific binding in vitro. Fluorescent cell images were taken by a confocal microscope. The human prostate cancer cells (PC3) were injected to five nude mice on hind limbs to make the xenograft tumor model. QD-antiVEGFR2 antibody complex was injected into the tumor model and fluorescence measurements were performed at 1, 4, 9, 12, 15, and 24 hours after the injection. RESULTS: The specific interaction between HUVECs and QD-antiVEGFR2 antibody was clearly shown in vitro. The in vivo fluorescence image disclosed that there was an increased signal of tumor, 12 hours after the injection of QDs. CONCLUSION: By showing endothelial cells binding with QDs-antiVEGFR2 antibodyand an experimental application of the antibody for VEGFR2 imaging in the prostate cancer xenograft mouse model, we suggests that the antibody-conjugated QDs can be a potential imaging tool for angiogenesis of the cancer.

Kwon, S., et al. (2015). "Automated measurement of multiple cancer biomarkers using quantum-dot-based microfluidic immunohistochemistry." Anal Chem **87**(8): 4177-4183.

We report an automated multiple biomarker measurement method for tissue from cancer patients using quantum dot (QD)-based protein detection combined with reference-based protein quantification and autofluorescence (AF) removal. For multiplexed detection of biomarkers in tissue samples, visualization of QDs on cytokeratin was performed to create a multichannel microfluidic device on sites with dense populations of tumor cells. Three major breast cancer biomarkers (i.e., estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2) were labeled using QDs successively on cancer cells in tissue sections. For the automated measurement of biomarkers, a cytokeratin-based biomarker normalization method was used to measure the averaged expression of proteins. A novel AF-removal algorithm was developed, which normalizes the reference AF spectra reconstructed from unknown AF spectra based on random sampling. For accurate quantification of QDs, we automatically and accurately removed the AF signal from 344 spots of QD-labeled tissue samples using 240 reference AF spectra. Using analytical data with 10 tissue samples from breast cancer patients, the measured biomarker intensities were in good agreement with the results of conventional analyses.

Kwon, S., et al. (2014). "A quantum dot-based microfluidic multi-window platform for quantifying the biomarkers of breast cancer cells." Integr Biol (Camb) **6**(4): 430-437.

Conventional molecular profiling methods using immunochemical assays have limits in terms of multiplexity and the quantification of biomarkers in investigation of cancer cells. In this paper, we demonstrate a quantum dot (QD)-based microfluidic multiple biomarker quantification (QD-MMBQ) method that enables labeling of more than eight proteins immunochemically on cell blocks within 1 h, in a quantitative manner. An internal reference, beta-actin, was used as a loading control to compensate for differences in not only the cell number but also in staining quality among specimens. Furthermore, the microfluidic blocking method exhibited less nonspecific binding of QDs than the conventional static blocking method.

Laster, M., et al. (2019). "When cancer meets quantum mechanics." Theor Biol Forum **112**(1-2): 35-51.

To date, classical deterministic Newtonian physics has been used by biologists to describe living processes. However, it is increasingly appreciated that the probabilistic view offered by quantum mechanics more accurately describes the behavior of atoms and materials in all systems. Here, we discuss how the concepts of quantum mechanics can be applied to biological processes involved in cancer. We present a concise summary inspired by Heisenberg's Uncertainty Principle to describe our <<Genetic Environmental Field Hypothesis>>. Combining the uncertainties of genetic changes as expressed by epigenetic changes and/or somatic mutations with the uncertainties of environmental changes, cells may become cancerous as a way to increase entropy. Throughout the paper we will utilize the H19 gene system as an example. Using the concepts of quantum mechanics to describe oncological processes may provide novel directions in our understanding of cancer.

Lee, B. H., et al. (2019). "Fluorescence intensity modulation of CdSe/ZnS quantum dots assesses reactive oxygen species during chemotherapy and radiotherapy for cancer cells." J Biophotonics **12**(2): e201800172.

Quantum dots (QDs) are semiconductor nanoparticles ranging in size from 2 to 10 nm. QDs are increasingly being developed for biomedical imaging, targeted drug delivery and green energy technology. These have led to much research on QD interactions with various physical, chemical and biological systems. For biological systems, research has focused on the biocompatibility/cytotoxicity of QDs in the context of imaging/therapy. However, there is a paucity of work on how biological systems and bioactive molecules might be used to alter the optoelectronic properties of QDs. Here, it is shown that these properties can be altered by reactive oxygen species (ROS) from chemotherapeutic media and biological cells following controlled changes in cellular activities. Using CdSe/ZnS core-shell QDs, spectroscopic analysis of optically excited QDs with HL60, K562 and T98G cancer cell lines is performed. Our results show statistically significant ($P < 0.0001$) modulation of the fluorescence emission spectra of the QDs due to the ROS produced by common chemotherapeutic drugs, daunorubicin and doxorubicin and by cells following chemotherapy/radiotherapy. This optical modulation, in addition to assessing ROS generation, will possibly enhance applications of QDs in simultaneous diagnostic imaging and nanoparticle-mediated drug delivery as well as simultaneous ROS assessment and radiosensitization for improved outcomes in cancer treatments. Reactive molecular species produced by biological cells and chemotherapeutic drugs can create electric fields that alter the photophysical properties of QDs, and this can be used for concurrent monitoring of cellular activities, while inducing changes in those cellular activities.

Lee, H., et al. (2017). "Optical coding of fusion genes using multicolor quantum dots for prostate cancer diagnosis." Int J Nanomedicine **12**: 4397-4407.

Recent studies have found that prostate cancer expresses abnormal genetic markers including multiple types of TMPRSS2-ERG fusion genes. The expression level of different TMPRSS2-ERG fusion genes is correlated to pathologic variables of aggressive prostate cancer and disease progression. State-of-the-art methods for detection of TMPRSS2-ERG fusion genes include reverse transcription polymerase chain reaction (RT-PCR) with a detection limit of 1 fmol at urinary condition. RT-PCR is time consuming, costly, and inapplicable for multiplexing. Ability to identify multiple fusion genes in a single sample has become important for diagnostic and clinical purposes. There is a need for a sensitive diagnostic test to detect multiple TMPRSS2-ERG fusion genes for an early diagnosis and prognosis of prostate cancer. Here, we propose to develop an assay for prostate cancer diagnosis using oligonucleotide-functionalized quantum dot and magnetic microparticle for optical detection of rearranged TMPRSS2-ERG fusion genes at a low concentration in urine. We found that our assay was able to identify three different types of fusion gene with a wide detection range and detection limit of 1 fmol (almost the same level of the RT-PCR result reported). Here, we show detection of multiple TMPRSS2-ERG fusion genes using color-coded oligonucleotides in cell lysate and urine.

Lee, J., et al. (2010). "Characterization and cancer cell specific binding properties of anti-EGFR antibody conjugated quantum dots." Bioconjug Chem **21**(5): 940-946.

Synthesis of biologically active antibody conjugated quantum dots (QDs) has been of great importance in cellular imaging and diagnostics. Cetuximab (or Erbitux) is the first monoclonal antibody drug which targets the epidermal growth factor receptor (EGFR) overexpressed in most cancer cells. In the present work, we investigated three different conjugation strategies to obtain the biologically functional QD-cetuximab conjugates for the tumor-specific imaging. Successful conjugation of cetuximab to QDs was achieved using PEG conjugated polymer-coated QDs and two long-chain heterobifunctional linkers, sulfo-LC-SPDP and sulfo-SMCC. The dissociation constant of the QD-cetuximab conjugates to EGFR was determined to be 0.61 +/- 0.28 nM. The cancer cell-specific binding ability of the QD-cetuximab conjugates was evaluated in vitro, and the cellular internalization of the QD-cetuximab conjugates was clearly demonstrated in live cells by confocal microscopy. The cellular imaging experiments using the QD-cetuximab conjugates showed a clear endocytosis pathway, which was evidenced by the colocalization of the QD-cetuximab conjugates with dye-labeled transferrin. These results suggest that the QD-cetuximab conjugates as an imaging modality for tumor EGFR overexpression can be expected to provide important information on the expression levels of EGFR on the cancer cells.

Lee, J., et al. (2015). "Simultaneous imaging of two different cancer biomarkers using aptamer-conjugated quantum dots." Sensors (Basel) **15**(4): 8595-8604.

Studying gene expression profile in a single cancer cell is important because multiple genes are associated with cancer development. Quantum dots (QDs) have been utilized as biological probes for imaging and detection. QDs display specific optical and electrical properties that depend on their size that can be applied for imaging and sensing applications. In this study, simultaneous imaging of the cancer biomarkers, tenascin-C and nucleolin, was performed using two types of aptamer-conjugated QDs. The simultaneous imaging of these two different cancer markers in three cancer cell lines was reliable and cell line-specific. Current requirements for cancer imaging technologies include the need for simple preparation methods and the ability to detect multiple cancer biomarkers and evaluate their intracellular localizations. The method employed in this study is a feasible solution to these requirements.

Lee, K. H., et al. (2012). "Quantitative molecular profiling of biomarkers for pancreatic cancer with functionalized quantum dots." Nanomedicine **8**(7): 1043-1051.

Applications in nanomedicine, such as diagnostics and targeted therapeutics, rely on the detection and targeting of membrane biomarkers. In this article we demonstrate absolute quantitative profiling, spatial mapping, and multiplexing of cancer biomarkers using functionalized quantum dots (QDs). We demonstrate highly selective targeting molecular markers for pancreatic cancer with extremely low levels of nonspecific binding. We confirm that we have saturated all biomarkers on the cell surface, and, in conjunction with control experiments, extract absolute quantitative values for the biomarker density in terms of the number of molecules per square micron on the cell surface. We show that we can obtain quantitative spatial information of biomarker distribution on a single cell, important because tumors' cell populations are inherently heterogeneous. We validate our quantitative measurements (number of molecules per square micron) using flow cytometry and demonstrate multiplexed quantitative profiling using color-coded QDs. FROM THE CLINICAL EDITOR: This paper demonstrates a nice example for quantum dot-based molecular targeting of pancreatic cancer cells for advanced high sensitivity

diagnostics and potential future selective therapeutic purposes.

Li, C., et al. (2014). "BRCAA1 antibody- and Her2 antibody-conjugated amphiphilic polymer engineered CdSe/ZnS quantum dots for targeted imaging of gastric cancer." Nanoscale Res Lett **9**(1): 244.

Successful development of safe and highly effective nanoprobes for targeted imaging of in vivo early gastric cancer is a great challenge. Herein, we choose the CdSe/ZnS (core-shell) quantum dots (QDs) as prototypical materials, synthesized one kind of a new amphiphilic polymer including dentate-like alkyl chains and multiple carboxyl groups, and then used the prepared amphiphilic polymer to modify QDs. The resultant amphiphilic polymer engineered QDs (PQDs) were conjugated with BRCAA1 and Her2 monoclonal antibody, and prepared BRCAA1 antibody- and Her2 antibody-conjugated QDs were used for in vitro MGC803 cell labeling and in vivo targeted imaging of gastric cancer cells. Results showed that the PQDs exhibited good water solubility, strong photoluminescence (PL) intensity, and good biocompatibility. BRCAA1 antibody- and Her2 antibody-conjugated QD nanoprobes successfully realized targeted imaging of in vivo gastric cancer MGC803 cells. In conclusion, BRCAA1 antibody- and Her2 antibody-conjugated PQDs have great potential in applications such as single cell labeling and in vivo tracking, and targeted imaging and therapeutic effects' evaluation of in vivo early gastric cancer cells in the near future.

Li, C. C., et al. (2021). "Development of a Single Quantum Dot-Mediated FRET Nanosensor for Sensitive Detection of Single-Nucleotide Polymorphism in Cancer Cells." Anal Chem **93**(43): 14568-14576.

Single-nucleotide polymorphisms (SNPs) are important hallmarks of human diseases. Herein, we develop a single quantum dot (QD)-mediated fluorescence resonance energy transfer (FRET) nanosensor with the integration of multiple primer generation rolling circle amplification (MPG-RCA) for sensitive detection of SNPs in cancer cells. This assay involves only a linear padlock probe for MPG-RCA. The presence of a mutant target facilitates the circularization of linear padlock probes to initiate RCA, producing three short single-stranded DNAs (ssDNAs) with the assistance of nicking endonuclease. The resulting ssDNAs can function as primers to induce cyclic MPG-RCA, resulting in the exponential amplification and generation of large numbers of linker probes. The linker probes can subsequently hybridize with the Cy5-labeled reporter probes and the biotinylated capture probes to obtain the sandwich hybrids. The assembly of these sandwich hybrids on the 605 nm-emission quantum dot (605QD) generates the 605QD-oligonucleotide-Cy5 nanostructures, resulting in efficient FRET from the 605QD to Cy5. This nanosensor is free from both the complicated probe design and the exogenous primers and has distinct advantages of high amplification efficiency, zero background signal, good specificity, and high sensitivity. It can detect SNPs with a large dynamic range of 8 orders of magnitude and a detection limit of 5.41 x 10(-20) M. Moreover, this nanosensor can accurately distinguish as low as 0.001% mutation level from the mixtures, which cannot be achieved by previously reported methods. Furthermore, it can discriminate cancer cells from normal cells and even quantify SNP at the single-cell level.

Li, C. F., et al. (2017). "Desmin detection by facile prepared carbon quantum dots for early screening of colorectal cancer." Medicine (Baltimore) **96**(5): e5521.

Th aim of this study was to develop a new facile chemical method for early screening of colorectal cancer.The -C(O)OH groups modified Carbon Quantum Dots (CQDs) were prepared by an facile innovative route of acid attacking on carbon nanotubes (CNTs). The -C(O)OH groups were further transported into -C(O)Cl groups by SOCl2 treating. The obtained ClCQDs were conjugated onto the anti-Desmin, which were applied for testing the Desmin concentration in serum by using linearly fitted relationship with photoluminescence (PL) intensity.The obtained carbon quantum dots are quasispherical graphite nanocrystals with photoluminescence at about 455 nm. The Desmin with concentration of 1 ng/mL can lead to a decrease of PL intensity for anti-Desmin conjugated CQDs with good linearity. This assay had good specificity for Desmin with in interferential substances of immunoglobulin G (IgG), alpha fetoprotein (AFP), and carcinoembryoic antigen (CEA).A new facile acid attack method was developed to prepare ClCQDs, which could conjugate onto the anti-Desmin for detection of Desmin in serum with high sensitivity and specificity. As the detection limit is lower than 1 ng/ mL, this work provides a promising strategy for the evaluation of colorectal cancer risk with low cost and excellent sensing performance.

Li, G., et al. (2021). "Identification and elimination of cancer cells by folate-conjugated CdTe/CdS Quantum Dots Chiral Nano-Sensors." Biochem Biophys Res Commun **560**: 199-204.

The specific identification and elimination of cancer cells has been a great challenge in the past few decades. In this study, the circular dichroism (CD) of cells was measured by a self-designed special system through the folate-conjugated chiral nano-sensor. A novel method was established to recognize cancer cells

from normal cells according to the chirality of cells based on their CD signals. After a period of interaction between the nano-sensor and cells, the sharp weakening of CD signals was induced in cancer cells but normal cells remained unchanged. The biocompatibility of the nano-sensor was evaluated and the result showed that it exhibited significant cytotoxic activity against cancer cells while no obvious damage on normal cells. Notably, the research indicated that the nano-sensor may selectively cause apoptosis in cancer cells, and thus, have the potential to act as an antitumor agent.

Li, G., et al. (2022). "Chiral FA Conjugated CdTe/CdS Quantum Dots for Selective Cancer Ablation." ACS Nano **16**(8): 12991-13001.

Inducing apoptosis in cancer cells is considered a potential therapeutic mechanism underlying cancers. Here, chiral folic acid (FA) conjugated Cys-CdTe/CdS quantum dots (QDs) conjugated with a cancer-targeting ligand were fabricated to induce apoptosis in vivo. Ligand-induced chirality mechanism for FA-Cys-CdTe/CdS QDs was discussed, which is verified by density functional theory (DFT) simulation. Interestingly, we found that the circular dichroism (CD) signals of chiral QDs can effectively distinguish breast cancer cells from normal cells, where a sharp decrease in CD signal and absorption intensity can be seen. Notably, chiral FA-Cys-CdTe/CdS QDs showed significant apoptosis-inducing ability after the release of mitochondrial apoptotic factors. Furthermore, in vivo experiments showed that chiral FA-Cys-CdTe/CdS QDs provide an efficient cancer ablation through the apoptosis process with negligible toxicity, demonstrating their great potential utility in targeted anticancer agent for future clinic application.

Li, H., et al. (2011). "Simultaneous detection of two lung cancer biomarkers using dual-color fluorescence quantum dots." Analyst **136**(7): 1399-1405.

Quantum dots (QDs) have the potential to simplify the performance of multiplexed analysis. In this work, a novel protocol for performing a simultaneous dual-protein immunoassay, i.e. two lung cancer biomarkers, carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE), based on dual-color QDs, is described. First, two capture antibodies (both with biotin tags), two antigens and two detection antibodies were mixed together and the sandwich complexes were thus formed in the homogeneous solution, and then streptavidin coated polystyrene beads were directly added into the resultant system. Bead aggregation can be made self-limiting by controlling the shaker speed during the immunoassay. A distinct transition occurs between limited and complete aggregation as a function of the shaker speed during the immunoassay. Second, dual-color QDs with emission maxima at 525 and 655 nm were added after washing and reacted with the corresponding detection antibodies. Third, the bead-QD conjugates were dissociated in the dissociation buffer and then free QDs were directly used for the fluorescence detection of CEA and NSE. The results show that CEA and NSE could be sensitively determined with a common 96-well fluorescence plate reader and with equal detection limits down to the 1.0 ng mL(-1) level. Within the calibrated amount, the protocol had excellent precision within 0.53% for each target and was comparable in performance to commercial single-analyte ELISAs. Furthermore, the proposed method has been successfully applied to the determination of dual markers in real samples without cross-reaction, and a good correlation was achieved after comparison with the conventional assay for CEA and NSE in 25 human serum samples.

Li, H., et al. (2022). "Cu-Doped black phosphorus quantum dots as multifunctional Fenton nanocatalyst for boosting synergistically enhanced H2O2-guided and photothermal chemodynamic cancer therapy." Nanoscale **14**(10): 3788-3800.

Chemodynamic therapy (CDT) is a cancer treatment that converts endogenous H2O2 into hydroxyl radicals (OH) through Fenton reaction to destroy cancer cells. However, there are still some challenges in accelerating the Fenton reaction of CDT and improving the biodegradability of nanocatalysts. Herein, a multifunctional biomimetic BPQDs-Cu@GOD (BCG) Fenton nanocatalyst for boosting synergistically enhanced H2O2-guided and photothermal CDT of cancer is reported. Cu(2+) in BCG can be reduced to Cu(+) by black phosphorus quantum dots (BPQDs), triggering a Cu(+)-mediated Fenton-like reaction to degrade H2O2 and generate abundant OH for cancer CDT. The loaded glucose oxidase (GOD) can consume the glucose in the tumor to produce abundant H2O2 for Fenton-like reaction. In addition, Cu(2+) in BCG can react with GSH in tumor cells to alleviate the antioxidant capacity of tumor tissues, further improving the CDT efficacy. Furthermore, the photothermal performance of BPQDs can be enhanced by capturing Cu(2+), improving the photoacoustic imaging and photothermal therapy (PTT) functions. More importantly, the enhanced photothermal performance can rapidly accelerate the Fenton-like reaction under NIR irradiation. Finally, Cu(2+) can accelerate the degradation of BPQDs, which can reduce the retention of reagents. As a novel multifunctional biocompatible Fenton nanocatalyst, BCG have great potential in cancer therapy.

Li, K., et al. (2017). "Effects of quantum dots on the ROS amount of liver cancer stem cells." Colloids Surf B Biointerfaces **155**: 193-199.

Liver cancer (LC) is a serious disease that threatens human lives. LC has a high recurrence rate and poor prognosis. LC stem cells (LCSCs) play critical roles in these processes. However, the mechanism remains unclear. Reactive oxygen species (ROS) can be used to determine cell apoptosis and proliferation. However, studies of the effects of exogenous nanomaterials on LCSC ROS changes are rarely reported. In this work, quantum dots (QDs) were prepared using a hydrothermal method, and QDs were further modified with polyethylene glycol (PEG) and bovine serum albumin (BSA) using a chemical approach. The effects of QDs, PEG-modified QDs (PEG@QDs) and BSA-modified QDs (BSA@QDs) on the amounts of ROS in liver cancer PLC/PRF/5 (PLC) cells and liver cancer stem cells (LCSCs) were principally investigated. The results showed that when the concentration of QDs, PEG@QDs, and BSA@QDs were 10nM and 90nM, the ROS amount in PLC cells increased by approximately 2- to 5-fold. However, when the concentrations of these nanomaterials were 10nM and 90nM, ROS levels in LCSCs were reduced by approximately 50%. This critical path potentially leads to drug resistance and recurrence of LC. This work provides an important indication for further study of LC drug resistance and recurrence.

Li, K., et al. (2018). "Recent Advances in the Cancer Bioimaging with Graphene Quantum Dots." Curr Med Chem **25**(25): 2876-2893.

Fluorescent graphene quantum dots (GQDs) have attracted increasing interest in cancer bioimaging due to their stable photoluminescence (PL), high stability, low cytotoxicity, and good biocompatibility. In this review, we present the synthesis and chemical modification of GQDs firstly, and then introduce their unique physical, chemical, and biological properties like the absorption, PL, and cytotoxicity of GQDs. Finally and most importantly, the recent applications of GQDs in cancer bioimaging are demonstrated in detail, in which we focus on the biofunctionalization of GQDs for specific cancer cell imaging and real-time molecular imaging in live cells. We expect this work would provide valuable guides on the synthesis and modification of GQDs with adjustable properties for various biomedical applications in the future.

Li, L., et al. (2012). "Quantum dot-aluminum phthalocyanine conjugates perform photodynamic reactions to kill cancer cells via fluorescence resonance energy transfer." Nanoscale Res Lett **7**(1): 386.

Sulfonated aluminum phthalocyanines (AlPcSs), commonly used photosensitizers for photodynamic therapy of cancers (PDT), were conjugated with amine-dihydrolipoic acid-coated quantum dots (QDs) by electrostatic binding, achieving 70 AlPcSs per QD. The AlPcS-QD conjugates can utilize the intense light absorptions of conjugated QDs to indirectly excite AlPcSs producing singlet oxygen via fluorescence resonance energy transfer (FRET), demonstrating a new excitation model for PDT. The AlPcS-QD conjugates easily penetrated into human nasopharyngeal carcinoma cells and carried out the FRET in cells, with efficiency around 80%. Under the irradiation of a 532-nm laser, which is at the absorption region of QDs but not fit for the absorption of AlPcSs, the cellular AlPcS-QD conjugates can destroy most cancer cells via FRET-mediated PDT, showing the potential of this new strategy for PDT.

Li, N., et al. (2013). "Quantum dot based fluorometric detection of cancer TF-antigen." Anal Chem **85**(20): 9699-9704.

Cancer is a major global health challenge that would benefit from advances in screening methods for early detection that are rapid and low cost. TF-antigen is a tumor-associated antigen displayed on cell surface proteins of a high percentage of human carcinomas. Here we present a fluorometric bioassay for TF-antigen (galactose-beta-(1-->3)-N-acetyl-d-galactosamine) that utilizes quantum dot (QD) technology coupled with magnetic beads for rapid detection of TF-antigen at high sensitivity (10(-7) M range). In the competitive bioassay, 4-aminophenyl beta-d-galactopyranoside (4-APG) conjugated to QDs competes with TF-antigen for binding sites on peanut agglutinin (PNA) that is immobilized on magnetic beads. The bioassay is specific and ultrasensitive in the environment of complex protein mixtures, demonstrating its potential applicability for the screening of clinical samples.

Li, R., et al. (2009). "Prognostic value of Akt-1 in human prostate cancer: a computerized quantitative assessment with quantum dot technology." Clin Cancer Res **15**(10): 3568-3573.

BACKGROUND: Akt/protein kinase B signaling pathway has been implicated in tumorigenesis and progression. Previous studies showed the predictive potential of p-Akt-1, but total Akt-1 could provide more reliable information. We used image deconvolution, nanotechnology (quantum dots), and image analysis to improve Akt-1 quantification. DESIGN: This tissue microarray study included 840 radical prostatectomy cases. Slides were incubated with primary antibody against nonphosphorylated Akt-1 (Akt-1) followed by biotinylated secondary antibody and then by Qdot655 streptavidin conjugate. Slides were imaged under fluorescence microscopy and spectral deconvolution (Nuance) and quantified using plug-in image analysis software. Average intensity of Akt-1 signal was measured and subject to statistical analysis. Multivariate analysis (Cox regression) was applied to assess the

prognostic value of Akt-1 for biochemical recurrence and prostate cancer-specific death. Akt-1 expression was also examined for correlations with Ki-67 index and apoptotic index in our database. RESULT: Akt-1 was inversely correlated with apoptotic index (rho = -0.203; P = 0.004) but not with Ki-67 index. The correlation between Akt and p-Akt is significant but weak (P = 0.0496; R(2) = 0.118). On multivariate analysis Akt-1 was independently predictive of biochemical recurrence [hazard ratio, 2.863 (95% confidence interval, 1.127-7.271); P = 0.0270]. Akt-1 level is also predictive of prostate cancer-specific death (P = 0.0376). CONCLUSION: High levels of Akt-1, assessed by quantum dots, deconvolution imaging, and image analysis, are associated with a higher risk of biochemical recurrence and prostate cancer-specific death.

Li, R. E., et al. (2018). "Graphene Quantum Dots Potently Block Copper-Mediated Oxidative DNA Damage: Implications for Cancer Intervention." React Oxyg Species (Apex) **6**(18): 406-413.

Our early work suggested that graphene quantum dots (GQDs) block Cu(II)/Cu(I) redox cycle in biological systems. Here we report that GQDs could also potently protect against copper redox-mediated oxidative DNA damage. Using Cu(II)/hydrogen peroxide, Cu(II)/hydroquinone, and Cu(II)/ascorbic acid as three biologically relevant systems for inducing oxidative DNA damage, we demonstrated that GQDs protected against the above system-induced DNA strand breaks in varphix-174 plasmid DNA in a concentration-dependent manner. Notably, a significant protection was observed with GQDs at 1 mug/ml, and a nearly complete protection was shown with 10 and 100 mug/ml of GQDs. Using electron paramagnetic resonance (EPR) spectrometry in conjunction with alpha-(4-pyridyl-1-oxide)-N-tert-butylnitrone (POBN)-spin trapping, we showed that the above three systems generated hydroxyl radicals, as evidenced by the formation of a POBN-CH3 radical adduct in the presence of 0.5 M dimethyl sulfoxide (DMSO). Consistent with the protective effects of GQDs on DNA damage, the hydroxyl radical formation was markedly reduced in the presence of GQDs in a concentration dependent manner. A nearly complete blockage of the hydroxyl radical generation was seen with GQDs at 10 and 100 mug/ml. Taken together, our results showed that GQDs potently protected against oxidative DNA damage. Considering the critical role of copper in cancer development, our findings might have important implications for cancer intervention with GQD-based nanotech modality.

Li, X., et al. (2020). "Combined photodynamic-chemotherapy investigation of cancer cells using carbon quantum dot-based drug carrier system." Drug Deliv **27**(1): 791-804.

The combined chemotherapy and photodynamic therapy have significant advantages for cancer treatments, which have higher therapeutic effects compared with other medicines. Herein, we focused on the synthesis of carbon quantum dot (CQD) based nanocarrier system. CQD and 5-aminolevulinic acid (5-ALA) were conjugated with mono-(5-BOC-protected-glutamine-6-deoxy) beta-cyclodextrin (CQD-Glu-beta-CD) moiety, and finally, the anticancer chemotherapy doxorubicin (DOX) drug was loaded in the 5-ALA-CQD-Glu-beta-CD system. The stepwise physicochemical changes for the preparation of the DOX loaded 5-ALA-CQD-Glu-beta-CD system were investigated by Fourier transform infrared (FT-IR) spectroscopy, X-ray diffraction (XRD), transmission electron microscopy (TEM), atomic force microscopy (AFM), and Raman fluorescence spectroscopy. The encapsulation efficiency of DOX in 5-ALA-CQD-Glu-beta-CD was observed at approximately 83.0%, and the loading capacity of DOX is approximately 20.37%. The in vitro releasing of DOX and 5-ALA was observed through the UV-vis spectroscopy by the lambdamax value of 487 nm and 253 nm, respectively. By the investigation against the breast MCF-7 cancer cells, the high cytotoxicity and morphological changes of cancer cells were observed by the treating of DOX/5-ALA-CQD-Glu-beta-CD. The generation of reactive oxygen species (ROS) upon 635 nm (25 mW cm(-2)) for 15 min laser irradiation-induced improved the therapeutic effects. In vitro cellular uptake studies recommend the synthesized DOX/5-ALA-CQD-Glu-beta-CD nanocarrier could significantly enhance the cell apoptosis and assist in the MCF-7 cell damages. The result suggests a multifunctional therapeutic system for chemo/photodynamic synergistic effects on cancer therapy.

Li, Y., et al. (2012). "In vivo cancer targeting and imaging-guided surgery with near infrared-emitting quantum dot bioconjugates." Theranostics **2**(8): 769-776.

Early detection and subsequent complete surgical resection are among the most efficient methods for treating cancer. However, low detection sensitivity and incomplete tumor resection are two challenging issues. Nanoparticle-based imaging-guided surgery has proven promising for cancer-targeted imaging and subsequent debulking surgery. Particularly, the use of near infrared (NIR) fluorescent probes such as NIR quantum dots (QDs) allows deep penetration and high sensitivity for tumor detection. In this study, NIR-emitting CdTe QDs (maximum fluorescence emission peak at 728 nm) were synthesized with a high quantum yield (QY) of 38%. The tumor-specific QD bioconjugates were obtained by attaching cyclic Arg-Gly-Asp peptide (cRGD) to the surface of synthesized

QDs, and then injected into U87 MG tumor-bearing mice via tail veins for tumor-targeted imaging. The tumor and its margins were visualized and distinguished by NIR QD bioconjugates, and tumor resection was successfully accomplished via NIR guidance using a Fluobeam-700 NIR imaging system. Our work indicates that the synthesized tumor-specific NIR QDs hold great promise as a potential fluorescent indicator for intraoperative tumor imaging.

Li, Y., et al. (2017). "Multifunctional Nanoplatform Based on Black Phosphorus Quantum Dots for Bioimaging and Photodynamic/Photothermal Synergistic Cancer Therapy." ACS Appl Mater Interfaces **9**(30): 25098-25106.

A multifunctional nanoplatform based on black phosphorus quantum dots (BPQDs) was developed for cancer bioimaging and combined photothermal therapy (PTT) and photodynamic therapy (PDT). BPQDs were functionalized with PEG chains to achieve improved biocompatibility and physiological stability. The as-prepared nanoparticles exhibit prominent near-infrared (NIR) photothermal and red-light-triggered photodynamic properties. The combined therapeutic application of PEGylated BPQDs were then performed in vitro and in vivo. The results demonstrate that the combined phototherapy significantly promote the therapeutic efficacy of cancer treatment in comparison with PTT or PDT alone. BPQDs could also serve as the loading platform for fluorescent molecules, allowing reliable imaging of cancer cells. In addition, the low cytotoxicity and negligible side effects to main organs were observed in toxicity experiments. The theranostic characteristics of PEGylated BPQDs provide an uplifting potential for the future clinical applications.

Li, Y., et al. (2022). "Bright, Magnetic NIR-II Quantum Dot Probe for Sensitive Dual-Modality Imaging and Intensive Combination Therapy of Cancer." ACS Nano **16**(5): 8076-8094.

Improving the effectiveness of cancer therapy will require tools that enable more specific cancer targeting and improved tumor visualization. Theranostics have the potential for improving cancer care because of their ability to serve as both diagnostics and therapeutics; however, their diagnostic potential is often limited by tissue-associated light absorption and scattering. Herein, we develop CuInSe2@ZnS:Mn quantum dots (QDs) with intrinsic multifunctionality that both enable the accurate localization of small metastases and act as potent tumor ablation agents. By leveraging the growth kinetics of a ZnS shell on a biocompatible CuInSe2 core, Mn doping, and folic acid functionalization, we produce biocompatible QDs with high near-infrared (NIR)-II fluorescence efficiency up to 31.2%, high contrast on magnetic resonance imaging (MRI), and preferential distribution in 4T1 breast cancer tumors. MRI-enabled contrast of these nanoprobes is sufficient to timely identify small metastases in the lungs, which is critically important for preventing cancer spreading and recurrence. Further, exciting tumor-resident QDs with NIR light produces both fluorescence for tumor visualization through radiative recombination pathways as well as heat and radicals through nonradiative recombination pathways that kill cancer cells and initiate an anticancer immune response, which eliminates tumor and prevents tumor regrowth in 80% of mice.

Li, Z., et al. (2016). "DNA-Programmed Quantum Dot Polymerization for Ultrasensitive Molecular Imaging of Cancer Cells." Anal Chem **88**(19): 9355-9358.

Inorganic nanocrystals, such as quantum dots (QDs), hold great promise as molecular imaging contrast agents because of their superior optical properties. However, the molecular imaging sensitivity of these probes is far from optimized due to the lack of efficient and general method for molecular engineering of nanocrystal into effective bioprobes for signal-amplified imaging. Herein, we develop a strategy to boost the molecular imaging sensitivity of QDs over the limit by copolymerizing QDs and cell-binding aptamers into linear QD-aptamer polymers (QAPs) through DNA-programmed hybridization chain reaction. We show that the cancer cells treated with QAPs exhibit much stronger photoluminescence (PL) signal than those treated with QD-aptamer monomers (QAMs) because of multivalent binding and multi-QD-based signal amplification. The enhanced cell binding and imaging capacity of QAPs significantly improves imaging-based discrimination between different cancer cell types. This approach adds a new dimension for engineering inorganic nanoparticles into effective bioprobes for biomedical applications.

Li, Z., et al. (2006). "Immunofluorescent labeling of cancer cells with quantum dots synthesized in aqueous solution." Anal Biochem **354**(2): 169-174.

Thioglycolic-acid-stabilized CdTe quantum dots, synthesized directly in aqueous solution, are successfully conjugated with biotin and polyethylene glycol. Using these conjugates, we report the development of this kind of water-soluble quantum dot for immunofluorescent labeling of cancer cells. The results show that these conjugates have very low nonspecific binding and good stability against photobleaching, enabling them to be applied in many biological fields, such as cellular labeling, intracellular tracking, and other imaging applications.

Lian, S., et al. (2012). "A universal quantum dots-aptamer probe for efficient cancer detection and targeted imaging." J Nanosci Nanotechnol **12**(10): 7703-7708.

Targeted quantum dots have shown as an analytical and imaging tool for cancer detection and molecular imaging. Aptamers have recently been demonstrated as ideal candidates for molecular targeting applications. In the present work, quantum dots (QDs) were encapsulated with functional poly(ethylene glycol)-phospholipids to improve their solubility in water solution. The as-prepared QDs were then conjugated with the AS1411 aptamer recognizing the nucleolin overexpressed on cancer cell surface. The recognition of QD-Aptamer nanocomplex to breast cancer cells was demonstrated using confocal microscopy, and the viability of QDs-aptamer bioconjugate bound cells were not affected within 24 h, indicating that the probe was biocompatible and suitable for in vitro diagnostic assays and live cell imaging. Such well-defined aptamer-conjugated QDs nanoprobe was simple and universal to be extended to prepare various aptamer-nanoparticles hybrid systems for cancer targeting and molecular imaging applications.

Liang, J., et al. (2020). "Versatile Nanoplatform Loaded with Doxorubicin and Graphene Quantum Dots/Methylene Blue for Drug Delivery and Chemophotothermal/Photodynamic Synergetic Cancer Therapy." ACS Appl Bio Mater **3**(10): 7122-7132.

A versatile platform for nanodrug delivery and synergetic therapy is a promising therapeutic pattern for antitumor treatment in clinical biology. Here, we innovatively encapsulated graphene quantum dots (GQDs) or methylene blue (MB) together with doxorubicin (DOX) into the cores of poly lactic-co-glycolic acid (PLGA) nanoparticles coated with bovine serum albumin (BSA) based on the emulsion method to synthesize core-shell structure nanoparticles (GQDs@DOX/PB and MB@DOX/PB NPs). The GQDs@DOX/PB NPs exhibited excellent photothermal properties and stability under 808 nm laser irradiation. The in vitro chemophotothermal synergetic experiments manifested that the GQDs@DOX/PB NPs effectively cause the thermal ablation of tumor cells under NIR laser irradiation. Meanwhile, the in vitro chemophotodynamic synergetic experiments revealed that the MB@DOX/PB NPs could produce reactive oxygen species and showed outstanding antitumor efficacy under 660 nm laser irradiation. Consequently, the pH-responsive multifunctional nanoparticles prepared by a facile strategy have a high tumor cell-killing efficacy, manifesting excellent potential in synergistic therapy.

Liang, Z., et al. (2021). "Bio-Conjugated Quantum Dots for Cancer Research: Detection and Imaging." Front Oncol **11**: 749970.

Ultrasound, computed tomography, magnetic resonance, and gamma scintigraphy-based detection and bio-imaging technologies have achieved outstanding breakthroughs in recent years. However, these technologies still encounter several limitations such as insufficient sensitivity, specificity and security that limit their applications in cancer detection and bio-imaging. The semiconductor quantum dots (QDs) are a kind of newly developed fluorescent nanoparticles that have superior fluorescence intensity, strong resistance to photo-bleaching, size-tunable light emission and could produce multiple fluorescent colors under single-source excitation. Furthermore, QDs have optimal surface to link with multiple targets such as antibodies, peptides, and several other small molecules. Thus, QDs might serve as potential, more sensitive and specific methods of detection than conventional methods applied in cancer molecular targeting and bio-imaging. However, many challenges such as cytotoxicity and nonspecific uptake still exist limiting their wider applications. In the present review, we aim to summarize the current applications and challenges of QDs in cancer research mainly focusing on tumor detection, bio-imaging, and provides opinions on how to address these challenges.

Lin, Z., et al. (2014). "A novel aptamer functionalized CuInS2 quantum dots probe for daunorubicin sensing and near infrared imaging of prostate cancer cells." Anal Chim Acta **818**: 54-60.

In this paper, a novel daunorubicin (DNR)-loaded MUC1 aptamer-near infrared (NIR) CuInS2 quantum dot (DNR-MUC1-QDs) conjugates were developed, which can be used as a targeted cancer imaging and sensing system. After the NIR CuInS2 QDs conjugated with the MUC1 aptamer-(CGA)7, DNR can intercalate into the double-stranded CG sequence of the MUC1-QDs. The incorporation of multiple CG sequences within the stem of the aptamers may further increase the loading efficiency of DNR on these conjugates. DNR-MUC1-QDs can be used to target prostate cancer cells. We evaluated the capacity of MUC1-CuInS2 QDs for delivering DNR to cancer cells in vitro, and its binding affinity to MUC1-positive and MUC1-negative cells. This novel aptamer functionalized QDs bio-nano-system can not only deliver DNR to the targeted prostate cancer cells, but also can sense DNR by the change of photoluminescence intensity of CuInS2 QDs, which concurrently images the cancer cells. The quenched fluorescence intensity of MUC1-QDs was proportional to the concentration of DNR in the concentration ranges of 33-88 nmol L(-1). The detection limit (LOD) for DNR was 19 nmol L(-1). We demonstrate the specificity

and sensitivity of this DNR-MUC1-QDs probe as a cancer cell imaging, therapy and sensing system in vitro.

Liu, F., et al. (2020). "Quantum dot-pulsed dendritic cell vaccines plus macrophage polarization for amplified cancer immunotherapy." Biomaterials **242**: 119928.

Dendritic cell (DC) vaccines hold great potential in cancer immunotherapy, but the suboptimal design of DC vaccines and the immunosuppressive tumor microenvironment largely impair their anti-tumor efficacy. Here, quantum dot (QD) pulsed-DC vaccines integrating with tumor-associated macrophage polarization are developed for amplified anti-tumor immunity. Semiconductor QDs are engineered with diverse functions to act as fluorescence nanoprobes, immunomodulatory adjuvants, and nanocarriers to load tumor antigens and Toll-like receptor 9 agonists. The QD-pulsed DC vaccines enable spatiotemporal tracking of lymphatic drainage and efficacy evaluation of DC immunotherapy, and trigger potent immunoactivation. Specifically, designer DC vaccine plus macrophage polarization elicits potent immune response to stimulate innate and adaptive antitumor immunity and ameliorate the immunosuppressive tumor microenvironment. As a new combination therapy, this strategy greatly boosts antigen-specific T-cell immunity and thus strongly inhibits local tumor growth and tumor metastasis in vivo. This study may provide an applicable treatment for cancer immunotherapy.

Liu, F., et al. (2012). "Magnetic graphene nanosheets based electrochemiluminescence immunoassay of cancer biomarker using CdTe quantum dots coated silica nanospheres as labels." Talanta **99**: 512-519.

A highly sensitive electrochemiluminescence (ECL) immunosensor for the detection of prostate specific antigen (PSA) was designed using biofunctionalized magnetic graphene nanosheets (G@Fe(3)O(4)) as immunosensing probes and CdTe quantum dots coated silica nanospheres (Si/QDs) as signal amplification labels. In this work, a sandwich-type immunosensor was fabricated, which was assembled on the surface of indium tin oxide glass (ITO). The analyte was detected in a home-made flow injection ECL (FI-ECL) cell through the immunosensor. Owing to the signal amplification of G@Fe(3)O(4) composite and Si/QDs, the ECL measurement showed a great increase in detection signals compared with the unampli fi ed method. Under optimal conditions, a wide detection range (0.003-50 ng mL(-1)) and a low detection limit (0.72 pg mL(-1)) were obtained through the sandwich-type immunosensor. The proposed strategy successfully demonstrated a reproducible, speci fi c, and potent method that can be expanded to detect other proteins.

Liu, H., et al. (2018). "Synthesis of Luminescent Carbon Dots with Ultrahigh Quantum Yield and Inherent Folate Receptor-Positive Cancer Cell Targetability." Sci Rep **8**(1): 1086.

Carbon dots (CDs) have a wide range of applications in chemical, physical and biomedical research fields. We are particularly interested in the use of CDs as fluorescence nanomaterials for targeted tumor cell imaging. One of the important aspects of success is to enhance the fluorescence quantum yields (QY) of CDs as well as increase their targetability to tumor cells. However, most of the reported CDs are limited by relative low QY. In the current study, for the first time, one-step synthesis of highly luminescent CDs by using folic acid (FA) as single precursor was obtained in natural water through hydrothermal method. The as-prepared CDs exhibited QY as high as 94.5% in water, which is even higher than most of organic fluorescent dyes. The obtained CDs showed excellent photoluminescent activity, high photostability and favorable biocompatibility. The FA residuals in CDs led to extraordinary targetability to cancer cells and promoted folate receptor-mediated cellular uptake successfully, which holds a great potential in biological and bioimaging studies.

Liu, H., et al. (2013). "Supersandwich cytosensor for selective and ultrasensitive detection of cancer cells using aptamer-DNA concatamer-quantum dots probes." Anal Chem **85**(6): 3385-3392.

In this work, a signal amplification supersandwich strategy was developed for highly selective and sensitive detection of cancer cells using aptamer-DNA concatamer-quantum dots (QDs) probes. First of all, electrode materials denoted as MWCNTs@PDA@AuNPs were fabricated by multiwall carbon nanotubes (MWCNTs), gold nanoparticles (AuNPs), and polydopamine (PDA) using a layer-by-layer technique. Then, the prepared bases as matrices were applied to bind concanavalin A (Con A), resulting in high stability, bioactivity, and capability for cell capture. Meanwhile, aptamer-DNA concatamer-QDs were designed via DNA hybridization followed by covalent assembling, which incorporated the specific recognition of the aptamer with the signal amplification of the DNA concatamer and QDs. With aptamer-DNA concatamer-QDs as recognizing probes, the model cancer cells (CCRF-CEM cells) were detected using a MWCNTs@PDA@AuNPs modified electrode with trapped Con A by means of fluorescence and electrochemical methods. The proposed supersandwich cytosensor showed high sensitivity with the detection limit of 50 cells mL(-1). More importantly, it could distinguish cancer cells from normal cells, which indicated the promising applications of our method in clinical diagnosis and treatment of cancers.

Liu, J., et al. (2015). "Cytotoxicity assessment of functionalized CdSe, CdTe and InP quantum dots in two human cancer cell models." Mater Sci Eng C Mater Biol Appl **57**: 222-231.

The toxicity of quantum dots (QDs) has been extensively studied over the past decade. Some common factors that originate the QD toxicity include releasing of heavy metal ions from degraded QDs and the generation of reactive oxygen species on the QD surface. In addition to these factors, we should also carefully examine other potential QD toxicity causes that will play crucial roles in impacting the overall biological system. In this contribution, we have performed cytotoxicity assessment of four types of QD formulations in two different human cancer cell models. The four types of QD formulations, namely, mercaptopropionic acid modified CdSe/CdS/ZnS QDs (CdSe-MPA), PEGylated phospholipid encapsulated CdSe/CdS/ZnS QDs (CdSe-Phos), PEGylated phospholipid encapsulated InP/ZnS QDs (InP-Phos) and Pluronic F127 encapsulated CdTe/ZnS QDs (CdTe-F127), are representatives for the commonly used QD formulations in biomedical applications. Both the core materials and the surface modifications have been taken into consideration as the key factors for the cytotoxicity assessment. Through side-by-side comparison and careful evaluations, we have found that the toxicity of QDs does not solely depend on a single factor in initiating the toxicity in biological system but rather it depends on a combination of elements from the particle formulations. More importantly, our toxicity assessment shows different cytotoxicity trend for all the prepared formulations tested on gastric adenocarcinoma (BGC-823) and neuroblastoma (SH-SY5Y) cell lines. We have further proposed that the cellular uptake of these nanocrystals plays an important role in determining the final faith of the toxicity impact of the formulation. The result here suggests that the toxicity of QDs is rather complex and it cannot be generalized under a few assumptions reported previously. We suggest that one have to evaluate the QD toxicity on a case to case basis and this indicates that standard procedures and comprehensive protocols are urgently needed to be developed and employed for fully assessing and understanding the origins of the toxicity arising from different QD formulations.

Liu, J., et al. (2021). "CoFe2O4-Quantum Dots for Synergistic Photothermal/Photodynamic Therapy of Non-small-Cell Lung Cancer Via Triggering Apoptosis by Regulating PI3K/AKT Pathway." Nanoscale Res Lett **16**(1): 120.

Non-small-cell lung cancer (NSCLC) has become the second most diagnosed malignant tumors worldwide. As our long-term interests in seeking nanomaterials to develop strategies of cancer therapies, we herein constructed novel CoFe2O4-quantum dots (QDs) with outstanding synergistic photothermal/photodynamic property which suppressed NSCLC efficiently without apparent toxicity. We showed that the combination of CoFe2O4-QDs + NIR treatment induces apoptosis of NSCLC cells. In addition, the CoFe2O4-QDs + NIR treatment also promotes reactive oxygen species generation to trigger cell death through regulating PI3K/AKT pathway. Moreover, the CoFe2O4-QDs + NIR treatment successfully eliminates tumor xenografts in vivo without apparent toxic effects. Taken together, we reported that the novel nanomaterials CoFe2O4-QDs could exhibit enhanced synergistic photothermal therapy and photodynamic therapy effect on killing NSCLC without toxicity, which could be a promising photosensitizer for NSCLC therapy.

Liu, L., et al. (2016). "Bead-based microarray immunoassay for lung cancer biomarkers using quantum dots as labels." Biosens Bioelectron **80**: 300-306.

In this study, we developed a multiplex immunoassay system that combines the suspension and planar microarray formats within a single layer of polydimethylsiloxane (PDMS) using soft lithography technology. The suspension format was based on the target proteins forming a sandwich structure between the magnetic beads and the quantum dot (QD) probes through specific antibody-antigen interactions. The planar microarray format was produced by fabricating an array of micro-wells in PDMS. Each micro-well was designed to trap a single microbead and eventually generated a microbead array within the PDMS chamber. The resultant bead-based on-chip assay could be used for simultaneously detecting three lung cancer biomarkers-carcinoembryonic antigen (CEA), fragments of cytokeratin 19 (CYFRA21-1) and neuron-specific enolase (NSE)-in 10 mul of human serum, with a wide linear dynamic range (1.03-111 ng/mL for CEA and CYFRA21-1; 9.26-1000 ng/ml for NSE) and a low detection limit (CEA: 0.19 ng/ml; CYFRA21-1: 0.97 ng/ml; NSE: 0.37 ng/ml; S/N=3). Our micro-well chip does not require complex e-beam lithography or the reactive ion etching process as with existing micro-well systems, which rely on expensive focused ion beam (FIB) milling or optical fiber bundles. Furthermore, the current approach is easy to operate without extra driving equipment such as pumps, and can make parallel detection for multiplexing with rapid binding kinetics, small reagent consumption and low cost. This work has demonstrated the importance of the successful application of on-chip multiplexing sandwich assays for the detection of biomarker proteins.

Liu, L., et al. (2012). "Bioconjugated pluronic triblock-copolymer micelle-encapsulated quantum dots for targeted imaging of cancer: in vitro and in vivo studies." Theranostics **2**(7): 705-713.

Early in this study, CdTe/ZnS core/shell quantum dots (QDs) were encapsulated in carboxylated Pluronic F127 triblock polymeric micelle, to preserve the optical and colloidal stability of QDs in biological fluids. Folic acid (FA) was then conjugated to the surface of QDs for the targeted delivery of the QD formulation to the tumor site, by exploiting the overexpressed FA receptors (FARs) on the tumor cells. Cytotoxicity study demonstrated that the QD formulation has negligible in vitro toxicity. The in vitro study showed that the bioconjugated micelle-encapsulated QDs, but not the unconjugated QDs, were able to efficiently label Panc-1 cancer cells. In vivo imaging study showed that bioconjugated QDs were able to target tumor site after intravenous injection of the formulation in tumor-bearing mice.

Liu, P., et al. (2018). "Anti-cancer activities of allyl isothiocyanate and its conjugated silicon quantum dots." Sci Rep **8**(1): 1084.

Allyl isothiocyanate (AITC), a dietary phytochemical in some cruciferous vegetables, exhibits promising anticancer activities in many cancer models. However, previous data showed AITC to have a biphasic effect on cell viability, DNA damage and migration in human hepatoma HepG2 cells. Moreover, in a 3D co-culture of HUVEC with pericytes, it inhibited tube formation at high doses but promoted this at low doses, which confirmed its biphasic effect on angiogenesis. siRNA knockdown of Nrf2 and glutathione inhibition abolished the stimulation effect of AITC on cell migration and DNA damage. The biological activity of a novel AITC-conjugated silicon quantum dots (AITC-SiQDs) has been investigated for the first time. AITC-SiQDs showed similar anti-cancer properties to AITC at high doses while avoiding the low doses stimulation effect. In addition, AITC-SiQDs showed a lower and long-lasting activation of Nrf2 translocation into nucleus which correlated with their levels of cellular uptake, as detected by the intrinsic fluorescence of SiQDs. ROS production could be one of the mechanisms behind the anti-cancer effect of AITC-SiQDs. These data provide novel insights into the biphasic effect of AITC and highlight the application of nanotechnology to optimize the therapeutic potential of dietary isothiocyanates in cancer treatment.

Liu, Q., et al. (2011). "CdSe quantum dots as labels for sensitive immunoassay of cancer biomarker proteins by electrogenerated chemiluminescence." Analyst **136**(24): 5197-5203.

A sensitive and specific immunoassay method for detecting alpha-fetoprotein (AFP) based on electrogenerated chemiluminescence (ECL) was described. ECL could perform detection for a series of different concentrations of AFP. CdSe quantum dots (QDs) were used as labels and were linked to AFP antibody (anti-AFP, the secondary antibody, Ab2*). Immunoassay was carried out on a modified electrode using a sandwich assay approach, where anti-AFP (Ab1) was covalently bound to the surface of an Au electrode to be allowed to capture AFP specifically. Afterwards, Ab2* was allowed to bind selectively to the captured AFP. The non-specific adsorption was negligible. In the presence of H(2)O(2), the ECL intensity increased with the increase of AFP, which indicated that an immunosensor for AFP was constructed. The detection of AFP based on measuring the ECL intensity of CdSe without the enzyme and mediator can promote the stability of the immunosensor. The linear range of the AFP assay was from 0.002 to 32 ng mL(-1). Furthermore, the immunosensor showed high sensitivity, good precision, stability, and reproducibility and could be used for the detection of real samples with consistent results in comparison with those obtained by the enzyme-linked immunosorbent assay (ELISA) method. The strategy was successfully demonstrated as a simple, cost-effective, specific, and potential method to detect AFP in practical samples.

Liu, Q., et al. (2013). "Differentiation of cancer cell type and phenotype using quantum dot-gold nanoparticle sensor arrays." Cancer Lett **334**(2): 196-201.

We demonstrate rapid and efficient sensing of mammalian cell types and states using nanoparticle-based sensor arrays. These arrays are comprised of cationic quantum dots (QDs) and gold nanoparticles (AuNPs) that interact with cell surfaces to generate distinguishable fluorescence responses based on cell surface signatures. The use of QDs as the recognition elements as well as the signal transducers presents the potential for direct visualization of selective cell surface interactions. Notably, this sensor is unbiased, precluding the requirement of pre-knowledge of cell state biomarkers and thus providing a general approach for phenotypic profiling of cell states, with additional potential for imaging applications.

Liu, X. L., et al. (2011). "Quantum dots-based double-color imaging of HER2 positive breast cancer invasion." Biochem Biophys Res Commun **409**(3): 577-582.

It has been well recognized that human epidermal growth factor receptor 2 (HER2) level in breast cancer (BC) is closely related to the malignant biologic behaviors of the tumor, including invasion and metastasis. Yet, there has been a lack of directly observable evidence to support such notion. Here we

report a quantum dots (QDs)-based double-color imaging technique to simultaneously show the HER2 level on BC cells and the type IV collagen in the tumor matrix. In benign breast tumor, the type IV collagen was intact. With the increasing of HER2 expression level, there has been a progressive decrease in type IV collagen around the cancer nest. At HER2 (3+) expression level, there has virtually been a total destruction of type IV collagen. Moreover, HER2 (3+) BC cells also show direct invasion into the blood vessels. This novel imaging method provides direct observable evidence to support the theory that the HER2 expression level is directly related to BC invasion.

Liu, Y. S., et al. (2007). "pH-sensitive Photoluminescence of CdSe/ZnSe/ZnS Quantum Dots in Human Ovarian Cancer Cells." J Phys Chem C Nanomater Interfaces **111**(7): 2872-2878.

The photoluminescence of mercaptoacetic acid (MAA)-capped CdSe/ZnSe/ZnS semiconductor nanocrystal quantum dots (QDs) in SKOV-3 human ovarian cancer cells is pH-dependent, suggesting applications in which QDs serve as intracellular pH sensors. In both fixed and living cells the fluorescence intensity of intracellular MAA-capped QDs (MAA QDs) increases monotonically with increasing pH. The electrophoretic mobility of MAA QDs also increases with pH, indicating an association between surface charging and fluorescence emission. MAA dissociates from the ZnS outer shell at low pH, resulting in aggregation and loss of solubility, and this may also contribute to the MAA QD fluorescence changes observed in the intracellular environment.

Liu, Z., et al. (2020). "Involvement of autophagy in realgar quantum dots (RQDs) inhibition of human endometrial cancer JEC cells." PeerJ **8**: e9754.

Realgar (As4S4) has been used in traditional Chinese medicines for treatment of malignancies. The poor solubility of As4S4 hampered its clinical applications. Realgar quantum dots (RQDs) were developed to overcome these problems. Previous studies revealed that the RQDs were effective against endometrial cancer JEC cells and hepatocarcinoma HepG2 cells via inducing apoptosis.Apoptosis and autophagy are important programmed cell death pathways leading to anticancer effects. This study further examined effects of RQDs on autophagy, focusing on the formation of the autophagosome in JEC cells. CCK8 assay was used to examine cell proliferation. Flow cytometry was used to analyze cell cycle. Transmission electron microscopy (TEM) was used to examine the autophagy, cells were transfected with pEGFP-C3-MAP1LC3B plasmid to examine effects of RQDs on autophagosome via confocal microscope. Autophagy-related proteins were examined by Western blot. RQDs exhibited cytotoxicity in JEC cells in a concentration- and time- dependent manner. RQDs induced G2 and S phase arrest in JEC cells. RQDs significantly induced autophagy, with the double-membrane and autophagosome-like structures by TEM. The diffused distribution of pEGFP-C3-MAP1LC3B green fluorescence were become the punctuate pattern fluorescence after treatment with RQDs in cells transfected with pEGFP-C3-MAP1LC3B plasmid RQDs increased the expression of autophagyregulatory proteins LC3 I/II, Beclin-1, p62 and Atg12 in a concentration-dependent manner, similar to autophagy induced by serum starvation, except for p62, as induction of p62 is a characteristic of arsenic compounds. Taken together, the present study clearly demonstrated that RQDs can induce autophagy in JEC cells as one of mechanisms of anticancer effects, and indicated that RQDs may be developed as an autophagy inducer.

Lo, P. Y., et al. (2020). "GFP Plasmid and Chemoreagent Conjugated with Graphene Quantum Dots as a Novel Gene Delivery Platform for Colon Cancer Inhibition In Vitro and In Vivo." ACS Appl Bio Mater **3**(9): 5948-5956.

Scientists have studied intensively the gene delivery carriers for treating genetic diseases. However, there are challenges that impede the application of naked gene-based therapy at the clinical level, such as quick elimination of the circulation, lack of membrane penetrability, and poor endosome trapping. Herein, we develop graphene quantum dots (GQDs)-derivative nanocarriers and introduce polyethylenimine (PEI) to equip the system with enhanced biocompatibility and abundant functional groups for modification. In addition to carrying green fluorescent protein (GFP) as an example of gene delivery, this system covalently binds colon cancer cells targeted antibody and epidermal growth factor receptor (EGFR) to enhance cell membrane penetrability and cell uptake of nanocarriers. To achieve multistrategy cancer therapy, the anticancer drug doxorubicin (Dox) is noncovalently encapsulated to achieve pH-induced drug release at tumor sites and leaves space for further functional gene modification. This nanoparticle serves as a multifunctional gene delivery system, which facilitates improved cytotoxicity and longer-sustained inhibition capacity compared to free Dox treatments in colon cancer cells. Moreover, our GQD composites display compatible tumor suppression ability compared with the free Dox treatment group in xenograft mice experiment with significantly less toxicity. This GQD nanoplatform was demonstrated as a multifunctional gene delivery system that could contribute to treating other genetic diseases in the future.

Lotfollahzadeh, S., et al. (2022). "TRAIL/S-layer/graphene quantum dot nanohybrid enhanced stability and anticancer activity of TRAIL on colon cancer cells." Sci Rep **12**(1): 5851.

Tumor necrosis factor (TNF)-related apoptosis inducing ligand (TRAIL), known as a cytokine of the TNF superfamily, is considered a promising antitumor agent due to its ability to selectively induce apoptosis in a wide variety of cancer cells. However, failure of its successful translation into clinic has led to development of nano-based platforms aiming to improve TRAIL therapeutic efficacy. In this regard, we fabricated a novel TRAIL-S-layer fusion protein (S-TRAIL) conjugated with graphene quantum dots (GQDs) to benefit both the self-assembly of S-layer proteins, which leads to elevated TRAIL functional stability, and unique optical properties of GQDs. Noncovalent conjugation of biocompatible GQDs and soluble fusion protein was verified via UV-visible and fluorescence spectroscopy, size and zeta-potential measurements and transmission electron microscopy. The potential anticancer efficacy of the nanohybrid system on intrinsically resistant cells to TRAIL (HT-29 human colon carcinoma cells) was investigated by MTT assay and flow cytometry, which indicated about 80% apoptosis in cancer cells. These results highlight the potential of TRAIL as a therapeutic protein that can be extensively improved by taking advantage of nanotechnology and introduce S-TRAIL/GQD complex as a promising nanohybrid system in cancer treatment.

Luo, G., et al. (2012). "Quantum dots in cancer therapy." Expert Opin Drug Deliv **9**(1): 47-58.

INTRODUCTION: Quantum dots (QDs) are nanometer-size luminescent semiconductor nanocrystals. Their unique optical properties, such as high brightness, long-term stability, simultaneous detection of multiple signals and tunable emission spectra, make them appealing as potential diagnostic and therapeutic systems in the field of oncology. AREAS COVERED: This paper summarizes the recent progress of promising applications of QDs in cancer therapy, from the following aspects: identifying molecular targets, sentinel lymph-node mapping, surgical oncology, drug delivery and tracking, fluorescence resonance energy transfer and photodynamic therapy, personalized and predictive medicine, and multifunctional design and development. Limitations and toxicity issues related to QDs in living organisms are also discussed. EXPERT OPINION: Bioconjugated QDs can be used to identify potential molecular biomarkers for cancer diagnosis, treatment and prognosis. They may allow the surgeon to map sentinel lymph nodes and perform a complete surgical resection. Their unique optical properties make them ideal donors of fluorescence resonance energy transfer and photodynamic therapy studies. Multifunctional QDs have become effective materials for synchronous cancer diagnosis, targeting and treatment. For QDs, toxicity remains the major barrier to clinical translation.

Luo, M., et al. (2019). "Folic Acid-Functionalized Black Phosphorus Quantum Dots for Targeted Chemo-Photothermal Combination Cancer Therapy." Pharmaceutics **11**(5).

Due to the inherent limitations, single chemo or photothermal therapies (PTT) are always inefficient. The combination of chemotherapy and PTT for the treatment of cancers has attracted a great interest during the past few years. As a photothermal agent, black phosphorus quantum dots (BPQDs) possess an excellent extinction coefficient, high photothermal conversion efficacy, and good biocompatibility. Herein, we developed a photo- and pH-sensitive nanoparticle based on BPQDs for targeted chemo-photothermal therapy. Doxorubicin (DOX) was employed as a model drug. This nanosystem displayed outstanding photothermal performance both in vitro and in vivo. Folic acid conjugation onto the surface endowed this system an excellent tumor-targeting effect, which was demonstrated by the cellular targeting assay. The BPQDs-based drug delivery system exhibited pH- and photo-responsive release properties, which could reduce the potential damage to normal cells. The in vitro cell viability study showed a synergistic effect in suppressing cancer cell proliferation. Therefore, this BPQDs-based drug delivery system has substantial potential for future clinical applications.

Lv, X. G., et al. (2013). "Clinical significance of EBP50 overexpression assessed by quantum dot analysis in gastric cancer." Oncol Lett **5**(6): 1844-1848.

Ezrin-radixin-moesin-binding phosphoprotein 50 (EBP50) is a postsynaptic density-95/disc-large/zonula occludens-1 (PDZ) homologous domain-containing protein that is involved in cell signaling. EBP50 regulates cell apoptosis, proliferation and invasion. In the present study, the prognostic impact factor of EBP50 expression was evaluated using a quantum dot (QD)-based assay and immunohistochemistry (IHC). The EBP50 protein expression in gastric cancer (GC) tissues was evaluated using IHC and QD-IHC. The study included 101 patients with GC (29 females and 72 males, aged 24-81 years), diagnosed and treated at the General Surgery Department of Renmin Hospital of Wuhan University (Wuhan, China) between 2000 and 2005. The survival rate was calculated using the Kaplan-Meier method and log-rank tests. IHC and QD analyses of 101 GC tissue specimens revealed that EBP50-positive tumor cells were frequently present in GC. Increased EBP50 immunostaining was observed in 63 specimens (62.4%).

The EBP50 expression levels were correlated with increased tumor size and the male gender. EBP50 was well distributed in the cytoplasm and nuclei of the GC cells. However, EBP50 protein expression exhibited no correlation with age, differentiation, stage or lymph node metastasis. There were no associations between the expression of EBP50 and the mean survival rates (IHC, 50.5 vs. 58.1 months, P>0.05; QD, 55.4 vs. 63.2 months, P>0.05). These findings suggest that EBP50 protein expression is not correlated with the prognosis of patients with GC. QD-IHC and IHC have similar advantages for the detection of EBP50 protein expression.

Ma, H., et al. (2021). "New Cy5 photosensitizers for cancer phototherapy: a low singlet-triplet gap provides high quantum yield of singlet oxygen." Chem Sci **12**(41): 13809-13816.

Highly efficient triplet photosensitizers (PSs) have attracted increasing attention in cancer photodynamic therapy where photo-induced reactive oxygen species (ROSs, such as singlet oxygen) are produced via singlet-triplet intersystem crossing (ISC) of the excited photosensitizer to kill cancer cells. However, most PSs exhibit the fatal defect of a generally less-than-1% efficiency of ISC and low yield of ROSs, and this defect strongly impedes their clinical application. In the current work, a new strategy to enhance the ISC and high phototherapy efficiency has been developed, based on the molecular design of a thio-pentamethine cyanine dye (TCy5) as a photosensitizer. The introduction of an electron-withdrawing group at the meso-position of TCy5 could dramatically reduce the singlet-triplet energy gap (DeltaE st) value (from 0.63 eV to as low as 0.14 eV), speed up the ISC process (tau ISC = 1.7 ps), prolong the lifetime of the triplet state (tau T = 319 mus) and improve singlet oxygen ((1)O2) quantum yield to as high as 99%, a value much higher than those of most reported triplet PSs. Further in vitro and in vivo experiments have shown that TCy5-CHO, with its efficient (1)O2 generation and good biocompatibility, causes an intense tumor ablation in mice. This provides a new strategy for designing ideal PSs for cancer photo-therapy.

Ma, Q., et al. (2014). "A novel carboxymethyl chitosan-quantum dot-based intracellular probe for Zn2+ ion sensing in prostate cancer cells." Acta Biomater **10**(2): 868-874.

In this paper, we fabricated novel carboxymethyl chitosan-coated CdTe quantum dots (CMC-CdTe QDs) via the electrostatic interaction between amino groups in the carboxymethyl chitosan polymeric chains and carboxyl groups of the CdTe QDs. Carboxymethyl chitosan on the surface of CdTe QDs had strong binding ability with Zn(2+), resulting in the obvious enhancement of the photoluminescence of CdTe QDs. The photoluminescence intensity of CMC-CdTe QDs probe was proportional to the concentration of Zn(2+) in the range of 5.0 x 10(-6) to 5.0 x 10(-3) mol l(-1). The detection limit for Zn(2+) was 4.5 x 10(-6) mol l(-1). The experimental results indicate that the CMC-CdTe QDs possess favorable cell compatibility, good sensitivity and selectivity for intracellular Zn(2+) sensing, and are promising candidates for cellular imaging and sensing in prostate cancer cells. The present study also provides an approach for the further development of nanoprobes dedicated to intracellular sensing.

Ma, Q., et al. (2012). "Multilayered, core/shell nanoprobes based on magnetic ferric oxide particles and quantum dots for multimodality imaging of breast cancer tumors." Biomaterials **33**(33): 8486-8494.

Multilayered, core/shell nanoprobes (MQQ-probe) based on magnetic nanoparticles (MNPs) and quantum dots (QDs) have been successfully developed for multimodality tumor imaging. This MQQ-probe contains Fe(3)O(4) MNPs, visible-fluorescent QDs (600 nm emission) and near infrared-fluorescent QDs (780 nm emission) in multiple silica layers. The fabrication of the MQQ-probe involves the synthesis of a primer Fe(3)O(4) MNPs/SiO(2) core by a reverse microemulsion method. The MQQ-probe can be used both as a fluorescent probe and a contrast reagent of magnetic resonance imaging. For breast cancer tumor imaging, anti-HER2 (human epidermal growth factor receptor 2) antibody was conjugated to the surface of the MQQ-probe. The specific binding of the antibody conjugated MQQ-probe to the surface of human breast cancer cells (KPL-4) was confirmed by fluorescence microscopy and fluorescence-activated cell sorting analysis in vitro. Due to the high tissue permeability of near-infrared (NIR) light, NIR fluorescence imaging of the tumor mice (KPL-4 cells transplanted) was conducted by using the anti-HER2 antibody conjugated MQQ-probe. In vivo multimodality images of breast tumors were successfully taken by NIR fluorescence and T(2)-weighted magnetic resonance. Antibody conjugated MQQ-probes have great potential to use for multimodality imaging of cancer tumors in vitro and in vivo.

Ma, Y. Y., et al. (2015). "Folic acid functionalized ZnO quantum dots for targeted cancer cell imaging." Nanotechnology **26**(30): 305702.

Aqueous stable luminescent ZnO quantum dots (QDs) were successfully synthesized with primary amine groups on the surface, which were designed to conjugate with folic acid (FA) to produce the final ZnO-FA QDs. Such ZnO-FA QDs were able to target some specific cancer cells with overexpressed FA receptors on

the membranes and thus differentiate the MCF-7 cancer cells from the normal 293T cells. The nanoparticle uptaking experiments by different cells were carried out in parallel and tracked by confocal laser microscopy dynamically. The results confirmed the specificity of our ZnO-FA QDs towards the FA-receptor overexpressed cancer cells, which had potential for diagnosing cancers in vitro.

Malavika, J. P., et al. (2022). "Green synthesis of multifunctional carbon quantum dots: An approach in cancer theranostics." Biomater Adv **136**: 212756.

Carbon quantum dots (CQDs) have gained significant growing attention in the recent past due to their peculiar characteristics including smaller size, high surface area, photoluminescence, chemical stability, facile synthesis and functionalization possibilities. They are carbon nanostructures having less than 10 nm size with fluorescent properties. In recent years, the scientific community is curiously adopting biomass precursors for the preparation of CQDs over the chemical compounds. These biomass sources are sustainable, eco-friendly, inexpensive, widely available and convert waste into valuable materials. Hence in our work the fundamental understating of diverse fabrication methodologies of CQDs, and the types of raw materials employed in recent times, are all examined and correlated comprehensively. Their unique combination of remarkable properties, together with the ease with which they can be fabricated, makes CQDs as promising materials for applications in diverse biomedical fields, in particular for bio-imaging, targeted drug delivery and phototherapy for cancer treatment. The mechanism for luminescence is of considerable significance for leading the synthesis of CQDs with tunable fluorescence emission. Therefore, it is aimed to explore and provide an updated review on (i) the recent progress on the different synthesis methods of biomass-derived CQDs, (ii) the contribution of surface states or functional groups on the luminescence origin and (iii) its potential application for cancer theranostics, concentrating on their fluorescence properties. Finally, we explored the challenges in modification for the synthesis of CQDs from biomass derivatives and the future scope of CQDs in phototherapy for cancer theranostics.

Mallikourti, V., et al. (2019). "Optimal Phased-Array Signal Combination For Polyunsaturated Fatty Acids Measurement In Breast Cancer Using Multiple Quantum Coherence MR Spectroscopy At 3T." Sci Rep **9**(1): 9259.

Polyunsaturated fatty acid (PUFA), a key marker in breast cancer, is non-invasively quantifiable using multiple quantum coherence (MQC) magnetic resonance spectroscopy (MRS) at the expense of losing half of the signal. Signal combination for phased array coils provides potential pathways to enhance the signal to noise ratio (SNR), with current algorithms developed for conventional brain MRS. Since PUFA spectra and the biochemical environment in the breast deviate significantly from those in the brain, we set out to identify the optimal algorithm for PUFA in breast cancer. Combination algorithms were compared using PUFA spectra from 17 human breast tumour specimens, 15 healthy female volunteers, and 5 patients with breast cancer on a clinical 3 T MRI scanner. Adaptively Optimised Combination (AOC) yielded the maximum SNR improvement in specimens (median, 39.5%; interquartile range: 35.5-53.2%, $p < 0.05$), volunteers (82.4 +/- 37.4%, $p < 0.001$), and patients (median, 61%; range: 34-105%, $p < 0.05$), while independent from voxel volume (rho = 0.125, p = 0.632), PUFA content (rho = 0.256, p = 0.320) or water/fat ratio (rho = 0.353, p = 0.165). Using AOC, acquisition in patients is 1.5 times faster compared to non-noise decorrelated algorithms. Therefore, AOC is the most suitable current algorithm to improve SNR or accelerate the acquisition of PUFA MRS from breast in a clinical setting.

Manan, F. A. A., et al. (2021). "Drug Release Profiles of Mitomycin C Encapsulated Quantum Dots-Chitosan Nanocarrier System for the Possible Treatment of Non-Muscle Invasive Bladder Cancer." Pharmaceutics **13**(9).

Nanotechnology-based drug delivery systems are an emerging technology for the targeted delivery of chemotherapeutic agents in cancer therapy with low/no toxicity to the non-cancer cells. With that view, the present work reports the synthesis, characterization, and testing of Mn:ZnS quantum dots (QDs) conjugated chitosan (CS)-based nanocarrier system encapsulated with Mitomycin C (MMC) drug. This fabricated nanocarrier, MMC@CS-Mn:ZnS, has been tested thoroughly for the drug loading capacity, drug encapsulation efficiency, and release properties at a fixed wavelength (358 nm) using a UV-Vis spectrophotometer. Followed by the physicochemical characterization, the cumulative drug release profiling data of MMC@CS-Mn:ZnS nanocarrier (at pH of 6.5, 6.8, 7.2, and 7.5) were investigated to have the highest release of 56.48% at pH 6.8, followed by 50.22%, 30.88%, and 10.75% at pH 7.2, 6.5, and 7.5, respectively. Additionally, the drug release studies were fitted to five different pharmacokinetic models including pesudo-first-order, pseudo-second-order, Higuchi, Hixson-Crowell, and Korsmeyers-Peppas models. From the analysis, the cumulative MMC release suits the Higuchi model well, revealing the diffusion-controlled mechanism involving the correlation of cumulative drug release proportional to the function square root of time at equilibrium, with the correlation coefficient values (R(2)) of 0.9849, 0.9604, 0.9783, and 0.7989 for drug release at pH 6.5, 6.8, 7.2, and 7.5,

respectively. Based on the overall results analysis, the formulated nanocarrier system of MMC synergistically envisages the efficient delivery of chemotherapeutic agents to the target cancerous sites, able to sustain it for a longer time, etc. Consequently, the developed nanocarrier system has the capacity to improve the drug loading efficacy in combating the reoccurrence and progression of cancer in non-muscle invasive bladder diseases.

Mandal, G., et al. (2013). "Cadmium-free quantum dots as time-gated bioimaging probes in highly-autofluorescent human breast cancer cells." Chem Commun (Camb) **49**(6): 624-626.

We report cadmium-free, biocompatible (Zn)CuInS(2) quantum dots with long fluorescence lifetimes as superior bioimaging probes using time-gated detection to suppress cell autofluorescence and improve the signal : background ratio by an order of magnitude. These results will be important for developing non-toxic fluorescence imaging probes for ultrasensitive biomedical diagnostics.

Mansur, A. A., et al. (2016). "Bioengineered quantum dot/chitosan-tripeptide nanoconjugates for targeting the receptors of cancer cells." Int J Biol Macromol **82**: 780-789.

Nanobiomaterials can be engineered to recognize cancer-specific receptors at the cellular level for diagnostic and therapeutic purposes. In this work, we report the synthesis of novel multifunctional nanoconjugates composed of fluorescent inorganic semiconductor quantum dot (QD) cores and tripeptide-modified polysaccharide organic shells. These structures were designed for targeting and imaging the alphavbeta3 integrin receptors of cancer cells. Initially, chitosan was covalently bound with the RGD peptide using a crosslinker to form bioconjugates (RGD-chitosan), which were later utilized as capping ligands for the production of surface-functionalized CdS QDs via a single-step process in aqueous media at room temperature. These core-shell nanostructures were extensively characterized by UV-vis spectroscopy, photoluminescence (PL) spectroscopy, Fourier transform infrared spectroscopy (FTIR), transmission electron microscopy (TEM), zeta potential (ZP) and dynamic light scattering (DLS). The TEM images and the UV-vis absorption results indicated the formation of ultra-small CdS QD nanocrystals with average diameters between 2.0 and 3.0 nm. In addition, the PL results demonstrated that the nanobioconjugates exhibited intense green fluorescence under excitation. The CdS-RGD-chitosan systems were effective at specific targeting integrin when assayed in vitro using two model cell cultures, HEK 293 (non-cancerous human embryonic kidney cell) and SAOS (cancerous sarcoma osteogenic-derived cells) imaged using fluorescence microscopy.

Mansur, A. A., et al. (2014). "Fluorescent nanohybrids based on quantum dot-chitosan-antibody as potential cancer biomarkers." ACS Appl Mater Interfaces **6**(14): 11403-11412.

Despite undeniable advances in medicine in recent decades, cancer is still one of the main challenges faced by scientists and professionals in the health sciences as it remains one of the world's most devastating diseases with millions of fatalities and new cases every year. Thus, in this work, we endeavored to synthesize and characterize novel multifunctional immunoconjugates composed of quantum dots (QDs) as the fluorescent inorganic core and antibody-modified polysaccharide as the organic shell, focusing on their potential applications for in vitro diagnosis of non-Hodgkin lymphoma (NHL) cancer tumors. Chitosan was covalently conjugated with anti-CD20 polyclonal antibody (pAbCD20) via formation of amide bonds between amines and carboxyl groups. In the sequence, these biopolymer-antibody immunoconjugates were utilized as direct capping ligands for biofunctionalization of CdS QDs (CdS/chitosan-pAbCD20) using a single-step process in aqueous medium at room temperature. The nanostructures were characterized by UV-vis spectroscopy, photoluminescence spectroscopy (PL), FTIR, and transmission electron microscopy (TEM) with selected area electron diffraction. The TEM images associated with the UV-vis optical absorption results indicated formation of ultrasmall nanocrystals with average diameters in the range of 2.5-3.0 nm. Also, the PL results demonstrated that the immunoconjugates exhibited "green" fluorescent activity under ultraviolet excitation. Moreover, using in vitro laser light scattering immunoassay (LIA), the QDs/immunoconjugates have shown binding affinity against antigen CD20 (aCD20) expressed by lymphocyte-B cancer cells. In summary, innovative fluorescent nanoimmunoconjugate templates were developed with promising perspectives to be used in the future for detection and imaging of cancer tumors.

Mansur, A. A. P., et al. (2019). "Dual-functional supramolecular nanohybrids of quantum dot/biopolymer/chemotherapeutic drug for bioimaging and killing brain cancer cells in vitro." Colloids Surf B Biointerfaces **184**: 110507.

Glioblastoma (GBM) is the utmost aggressive and lethal primary brain cancer, which has a poor prognosis and remains virtually incurable. Nanomedicine with emerging disruptive nanotechnology alternatives, including designed supramolecular nanohybrids has excellent potential as multimodal tools against cancer by combining

nanomaterials, biomacromolecules, and drugs. Thus, we developed and constructed for the first time quantum dot-biopolymer-drug nanohybrids based on host-guest chemistry for simultaneous bioimaging, targeting, and anti-cancer drug delivery against GBM cells in vitro. ZnS fluorescent quantum dots (ZnS-QDs) were produced using chemically modified polysaccharide, carboxymethylcellulose (CMC), as water-soluble capping ligand and biofunctional layer via a facile one-step eco-friendly aqueous colloidal process at room temperature and physiological pH. These hybrid inorganic-organic nanocolloids (ZnS@CMC) were electrostatically conjugated with doxorubicin (DOX) anti-cancer drug forming innovative supramolecular complexes (ZnS@CMC-DOX) for amalgamating bioimaging and killing cancer cells. These nanoconjugates were characterized regarding their optical and physicochemical properties combined with morphological and structural features. The cytocompatibility was evaluated by MTT assay using healthy and GBM cells. The results showed that ultra-small ZnS-QDs were expertly produced uniform nanocolloids (average size=3.6nm). They demonstrated photoluminescence emission within the visible range of spectra. The cell viability results in vitro showed no cytotoxicity of ZnS@CMC nanohybrids towards both cell types. In summary, the novelty of this research relies on using a nanotheranostic strategy for developing ZnS@CMC-DOX nanohybrids with supramolecular vesicle-like structures. They behaved simultaneously as active fluorescent nanoprobes and nanocarriers with modulated drug release for bioimaging and killing malignant glioma cells proving the high potential for applications in cancer nanomedicine.

Mansur, A. A. P., et al. (2017). "Carboxymethylcellulose/ZnCdS fluorescent quantum dot nanoconjugates for cancer cell bioimaging." Int J Biol Macromol **96**: 675-686.

In this study, it is reported the use of sodium carboxymethyl cellulose (CMCel) as a multifunctional biocompatible polysaccharide for the direct synthesis of fluorescent alloyed-ZnCdS quantum dot (QD) nanoconjugates via aqueous "green" process at room temperature. The nanoconjugates were extensively characterized by spectroscopical (NMR, FTIR, UV-vis, PL) and morphological techniques (DLS, TEM) for accessing their structural and physicochemical properties associated with X-ray photoelectron spectroscopy (XPS) for surface and interface analysis. The results proved the hypothesis of formation of core-shell nanostructures composed by the semiconductor ZnCdS QD core and the organic biocompatible ligand CMCel shell. Moreover, CMCel chemical functional groups played a pivotal role for controlling the size of water-soluble colloidal nanocrystals (2r=4-5nm) and hydrodynamic diameters (<15nm) evidenced by metal complexation and interactions at the nanointerfaces. Additionally, these nanoconjugates were cytocompatible and luminescent for bioimaging human osteosarcoma cancer cells. Thus, these novel polysaccharide-based fluorescent bioconjugates offer promising perspectives as nanoplatforms for cancer cell bioimaging and diagnosis purposes.

Mansur, A. A. P., et al. (2018). "Fluorescent ZnS Quantum Dots-Phosphoethanolamine Nanoconjugates for Bioimaging Live Cells in Cancer Research." ACS Omega **3**(11): 15679-15691.

Many human diseases, including metabolic, immune, and central nervous system disorders, as well as several types of cancers, are the consequence of an important alteration in lipid-related metabolic biomolecules. Although recognized that one of the most important metabolic hallmarks of cancer cells is deregulation of lipid metabolism, the multiple complex signaling pathways are poorly understood yet. Thus, in this research, novel nanoconjugates made of ZnS quantum dots (QDs) were directly synthesized in aqueous media using phosphoethanolamine (PEA) as the capping ligand, which is an important biomolecule naturally present in cells for de novo biosynthesis of fatty acids and phospholipids involved in the cell structure (e.g., membrane), differentiation, and cancer growth. These QD-PEA bio-nanoconjugates were characterized by spectroscopical and morphological techniques. The results demonstrated that fluorescent ZnS nanocrystalline QDs were produced with uniform spherical morphology and estimated sizes of 3.3 +/- 0.6 nm. These nanoconjugates indicated core-shell colloidal nanostructures (ZnS QD-PEA) with the hydrodynamic diameter (H D) of 26.0 +/- 3.5 nm and zeta-potential centered at -30.0 +/- 4.5 mV. The cell viability response using mitochondrial activity assay in vitroconfirmed no cytotoxicity at several concentrations of PEA (biomolecule) and the ZnS-PEA nanoconjugates. Moreover, these nanoconjugates effectively behaved as fluorescent nanomarkers for tracking the endocytic pathways of cancer cells using confocal laser scanning microscopy bioimaging. Hence, these results proved that biofunctionalized ZnS-PEA nanoprobes offer prospective tools for cellular bioimaging with encouraging forecast for future applications as active fluorescent biomarker conjugates in metabolic-related cancer research.

Mansur, A. A. P., et al. (2022). "Carboxymethylcellulose biofunctionalized ternary quantum dots for subcellular-targeted brain cancer nanotheranostics." Int J Biol Macromol **210**: 530-544.

Among the most lethal forms of cancer, malignant brain tumors persist as one of the greatest

challenges faced by oncologists, where nanotechnology-driven theranostics can play a critical role in developing novel polymer-based supramolecular nanoarchitectures with multifunctional and multi-modal characteristics to fight cancer. However, it is virtually a consensus that, besides the complexity of active delivering anticancer drugs by the nanocarriers to the tumor site, the current evaluation methods primarily relying on in vitro assays and in vivo animal models have been accounted for the low translational effectiveness to clinical applications. In this view, the chick chorioallantoic membrane (CAM) assay has been increasingly recognized as one of the best preclinical models to study the effects of anticancer drugs on the tumor microenvironment (TME). Thus, in this study, we designed, characterized, and developed novel hybrid nanostructures encompassing chemically functionalized carboxymethylcellulose (CMC) with mitochondria-targeting pro-apoptotic peptide (KLA) and cell-penetrating moiety (cysteine, CYS) with fluorescent inorganic semiconductor (Ag-In-S, AIS) for simultaneously bioimaging and inducing glioblastoma cancer cell (U-87 MG, GBM) death. The results demonstrated that the CMC-peptide macromolecules produced supramolecular vesicle-like nanostructures with aqueous colloidal stability suitable as nanocarriers for passive and active targeting of cancer tumors. The optical properties and physicochemical features of the nanoconjugates confirmed their suitability as photoluminescent nanoprobes for cell bioimaging and intracellular tracking. Moreover, the results in vitro demonstrated a notable killing activity towards GBM cells of cysteine-bearing CMC conjugates coupled with pro-apoptotic KLA peptides. More importantly, compared to doxorubicin (DOX), a model anticancer drug in chemotherapy that is highly toxic, these innovative nanohybrids nanoconjugates displayed higher lethality against U-87 MG cancer cells. In vivo CAM assays validated these findings where the nanohybrids demonstrated a significant reduction of GBM tumor progression (41% area) and evidenced an antiangiogenic activity. These results pave the way for developing polymer-based hybrid nanoarchitectonics applied as targeted multifunctional theranostics for simultaneous imaging and therapy against glioblastoma while possibly reducing the systemic toxicity and side-effects of conventional anticancer chemotherapeutic agents.

Mansur, H. S., et al. (2015). "Water-soluble nanoconjugates of quantum dot-chitosan-antibody for in vitro detection of cancer cells based on "enzyme-free" fluoroimmunoassay." Mater Sci Eng C Mater Biol Appl **52**: 61-71.

Cancer remains one of the world's most devastating diseases with millions of fatalities and new cases every year. In this work, we attempted to develop a facile "enzyme-free" fluoroimmunoassay based on the novel nanoconjugates composed of CdS quantum dots (QDs) as the fluorescent inorganic core and an antibody-modified polysaccharide as the organic shell, modeling their possible application for the in vitro diagnosis of non-Hodgkin lymphoma (NHL) cancer. Chitosan was conjugated with an anti-CD20 polyclonal antibody (pAbCD20) by the formation of covalent amide bonds. In the sequence, these chitosan-antibody conjugates were utilized as direct ligands for the surface biofunctionalization of CdS QDs (CdS/chitosan-pAbCD20) using a single-step colloidal process in aqueous medium at room temperature. The most relevant physico-chemical properties of these nanoconjugates were assessed by morphological and spectroscopic techniques. The results indicated that CdS nanocrystals were produced with an average diameter of 2.5 nm and with cubic zinc blende crystalline nanostructure. The CdS-immunoconjugates (CdS/chitosan-pAbCD20) presented colloidal hydrodynamic diameter (HD) of 15.0 +/- 1.2n m. In addition, the results evidenced that the "enzyme-free" QD-linked immunosorbent assay (QLISA) was effective for the in vitro detection against the antigen CD20 (aCD20) based on fluorescent behavior of the CdS nanoconjugates. Moreover, the CdS-immunoconjugates were successfully used for fluorescence bioimaging of NHL cancer cells. Finally, the cell viability results using different cell cultures based on LDH, MTT and Resazurin bio-assays have demonstrated no cytotoxicity of the new CdS-chitosan bioconjugates relative to the standard controls. Thus, CdS conjugates may offer a promising platform for the future development of in vitro and in vivo applications for the detection and diagnosis of NHL cancer cells.

Manzoor, K., et al. (2009). "Bio-conjugated luminescent quantum dots of doped ZnS: a cyto-friendly system for targeted cancer imaging." Nanotechnology **20**(6): 065102.

A heavy-metal-free luminescent quantum dot (QD) based on doped zinc sulfide (ZnS), conjugated with a cancer-targeting ligand, folic acid (FA), is presented as a promising bio-friendly system for targeted cancer imaging. Doped QDs were prepared by a simple aqueous method at room temperature. X-ray diffraction and transmission electron microscopy studies showed the formation of monodisperse QDs of average size approximately 4 nm with cubic (sphalerite) crystal structure. Doping of the QDs with metals (Al(3+)), transition metals (Cu(+), Mn(2+)) and halides (F(-)) resulted in multi-color emission with dopant-specific color tunability ranging from blue (480 nm) to red (622 nm). Luminescent centers in doped QDs could be excited using bio-friendly visible light >400 nm by directly populating the dopant centers, leading to bright

emission. The cytotoxicity of bare and FA conjugated QDs was tested in vitro using normal lung fibroblast cell line (L929), folate-receptor-positive (FR+) nasopharyngeal epidermoid carcinoma cell line (KB), and FR-negative (FR-) lung cancer cell line (A549). Both bare and FA-conjugated ZnS QDs elicited no apparent toxicity even at high concentrations of approximately 100 microM and 48 h of incubation. In contrast, CdS QDs prepared under identical conditions showed relatively high toxicity even at low concentrations of approximately 0.1 microM and 24 h of incubation. Interaction of FA-QDs with different cell lines showed highly specific attachment of QDs in the FR+ cancer cell line, leaving others unaffected. The bright and stable luminescence of the QDs could be used to image both single cancer cells and colonies of cancer cells without affecting their metabolic activity and morphology. Thus, this study presents, for the first time, the use of non-toxic, Cd-, Te-, Se-, Pb- and Hg-free luminescent QDs for targeted cancer imaging.

Martins, C. S. M., et al. (2022). "Quantum Dots for Cancer-Related miRNA Monitoring." ACS Sens **7**(5): 1269-1299.

Quantum dots (QDs) possess exceptional optoelectronic properties that enable their use in the most diverse applications, namely, in the medical field. The prevalence of cancer has increased and has been considered the major cause of death worldwide. Thus, there has been a great demand for new methodologies for diagnosing and monitoring cancer in cells to provide an earlier prognosis of the disease and contribute to the effectiveness of treatment. Several molecules in the human body can be considered relevant as cancer markers. Studies published over recent years have revealed that micro ribonucleic acids (miRNAs) play a crucial role in this pathology, since they are responsible for some physiological processes of the cell cycle and, most important, they are overexpressed in cancer cells. Thus, the analytical sensing of miRNA has gained importance to provide monitoring during cancer treatment, allowing the evaluation of the disease's evolution. Recent methodologies based on nanochemistry use fluorescent quantum dots for sensing of the miRNA. Combining the unique characteristics of QDs, namely, their fluorescence capacity, and the fact that miRNA presents an aberrant expression in cancer cells, the researchers created diverse strategies for miRNA monitoring. This review aims to present an overview of the recent use of QDs as biosensors in miRNA detection, also highlighting some tutorial descriptions of the synthesis methods of QDs, possible surface modification, and functionalization approaches.

Mashinchian, O., et al. (2014). "Impacts of quantum dots in molecular detection and bioimaging of cancer." Bioimpacts **4**(3): 149-166.

INTRODUCTION: A number of assays have so far been exploited for detection of cancer biomarkers in various malignancies. However, the expression of cancer biomarker(s) appears to be extremely low, therefore accurate detection demands sensitive optical imaging probes. While optical detection using conventional fluorophores often fail due to photobleaching problems, quantum dots (QDs) offer stable optical imaging in vitro and in vivo. METHODS: In this review, we briefly overview the impacts of QDs in biology and its applications in bioimaging of malignancies. We will also delineate the existing obstacles for early detection of cancer and the intensifying use of QDs in advancement of diagnostic devices. RESULTS: Of the QDs, unlike the II-VI type QDs (e.g., cadmium (Cd), selenium (Se) or tellurium (Te)) that possess inherent cytotoxicity, the I-III-VI 2 type QDs (e.g., AgInS2, CuInS2, ZnS-AgInS2) appear to be less toxic bioimaging agents with better control of band-gap energies. As highly-sensitive bioimaging probes, advanced hybrid QDs (e.g., QD-QD, fluorochrome-QD conjugates used for sensing through fluorescence resonance energy transfer (FRET), quenching, and barcoding techniques) have also been harnessed for the detection of biomarkers and the monitoring of delivery of drugs/genes to the target sites. Antibody-QD (Ab-QD) and aptamer- QD (Ap-QD) bioconjugates, once target the relevant biomarker, can provide highly stable photoluminescence (PL) at the target sites. In addition to their potential as nanobiosensors, the bioconjugates of QDs with homing devices have successfully been used for the development of smart nanosystems (NSs) providing targeted bioimaging and photodynamic therapy (PDT). CONCLUSION: Having possessed great deal of photonic characteristics, QDs can be used for development of seamless multifunctional nanomedicines, theranostics and nanobiosensors.

Maxwell, T., et al. (2015). "Non-Cytotoxic Quantum Dot-Chitosan Nanogel Biosensing Probe for Potential Cancer Targeting Agent." Nanomaterials (Basel) **5**(4): 2359-2379.

Quantum dot (Qdot) biosensors have consistently provided valuable information to researchers about cellular activity due to their unique fluorescent properties. Many of the most popularly used Qdots contain cadmium, posing the risk of toxicity that could negate their attractive optical properties. The design of a non-cytotoxic probe usually involves multiple components and a complex synthesis process. In this paper, the design and synthesis of a non-cytotoxic Qdot-chitosan nanogel composite using straight-

forward cyanogen bromide (CNBr) coupling is reported. The probe was characterized by spectroscopy (UV-Vis, fluorescence), microscopy (Fluorescence, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Dynamic Light Scattering. This activatable ("OFF"/"ON") probe contains a core-shell Qdot (CdS:Mn/ZnS) capped with dopamine, which acts as a fluorescence quencher and a model drug. Dopamine capped "OFF" Qdots can undergo ligand exchange with intercellular glutathione, which turns the Qdots "ON" to restore fluorescence. These Qdots were then coated with chitosan (natural biocompatible polymer) functionalized with folic acid (targeting motif) and Fluorescein Isothiocyanate (FITC; fluorescent dye). To demonstrate cancer cell targetability, the interaction of the probe with cells that express different folate receptor levels was analyzed, and the cytotoxicity of the probe was evaluated on these cells and was shown to be nontoxic even at concentrations as high as 100 mg/L.

McHugh, K. J., et al. (2018). "Biocompatible Semiconductor Quantum Dots as Cancer Imaging Agents." Adv Mater **30**(18): e1706356.

Approximately 1.7 million new cases of cancer will be diagnosed this year in the United States leading to 600 000 deaths. Patient survival rates are highly correlated with the stage of cancer diagnosis, with localized and regional remission rates that are much higher than for metastatic cancer. The current standard of care for many solid tumors includes imaging and biopsy with histological assessment. In many cases, after tomographical imaging modalities have identified abnormal morphology consistent with cancer, surgery is performed to remove the primary tumor and evaluate the surrounding lymph nodes. Accurate identification of tumor margins and staging are critical for selecting optimal treatments to minimize recurrence. Visible, fluorescent, and radiolabeled small molecules have been used as contrast agents to improve detection during real-time intraoperative imaging. Unfortunately, current dyes lack the tissue specificity, stability, and signal penetration needed for optimal performance. Quantum dots (QDs) represent an exciting class of fluorescent probes for optical imaging with tunable optical properties, high stability, and the ability to target tumors or lymph nodes based on surface functionalization. Here, state-of-the-art biocompatible QDs are compared with current Food and Drug Administration approved fluorophores used in cancer imaging and a perspective on the pathway to clinical translation is provided.

Meng, H., et al. (2011). "Conjugates of folic acids with BSA-coated quantum dots for cancer cell targeting and imaging by single-photon and two-photon excitation." J Biol Inorg Chem **16**(1): 117-123.

Bovine serum albumin (BSA)-coated CdTe/ZnS quantum dots (BSA-QDs) were selected to conjugate with folic acid (FA), forming FA-BSA-QDs. This study aims to develop these small FA-BSA-QDs (less than 10 nm) for the diagnosis of cancers in which the FA receptor (FR) is overexpressed. The enhancement of cellular uptake in FR-positive human nasopharyngeal carcinoma cells (KB cells) for FA-BSA-QDs was found by means of confocal fluorescence microscopy under single-photon and two-photon excitation. The uptake enhancement for FA-BSA-QDs was further evaluated by flow-cytometric analysis in 10(4) KB cells, and was about 3 times higher than for BSA-QDs on average. The uptake enhancement was suppressed when KB cells had been pretreated with excess FA, reflecting that the enhancement was mediated by the association of FR at cell membranes with FA-BSA-QDs. When human embryonic kidney cells (293T) (FR-negative cells) and KB cells, respectively, were incubated with FA-BSA-QDs (1 muM) for 40 min, the FA-BSA-QD uptake by 293T cells was much weaker than that by KB cells, demonstrating that FA-BSA-QDs could undergo preferential binding on FR-positive cancer cells. These characteristics suggest that FA-BSA-QDs are potential candidates for cancer diagnosis.

Meng, X., et al. (2019). "Electrochemiluminescent immunoassay for the lung cancer biomarker CYFRA21-1 using MoOx quantum dots." Mikrochim Acta **186**(12): 855.

Molybdenum oxide quantum dots (MoOx QDs) were synthesized by a one-pot method and used as a versatile probe in an electrochemiluminescent (ECL) immunoassay of the non-small cell lung cancer biomarker cytokeratin 19 fragment 21-1 (CYFRA21-1) as a model analyte. The MoOx QDs exhibited stable and strong cathodic green ECL, with an emission peak at 535 nm, in the presence of K2S2O8 within the potential range of -2.0 to 0 V. On exposure to CYFRA21-1, the ECL decreases because of the immunoreaction between CYFRA21-1 and its antibody which generates a barrier for electron transfer. The determination of CYFRA21-1 with favorable analytical performances was successfully realized under the optimal conditions. ECL decreases linearly in the 1 pg mL(-1) to 350 ng mL(-1) CYFRA21-1 concentration range, and the detection is as low as 0.3 pg mL(-1). Excellent recoveries from CYFRA21-1-spiked human serum indicate that the assay can be operated under physiological conditions. Graphical abstractSchematic representation of the fabrication of molybdenum oxide quantum dots (MoOx QDs) and the electrochemiluminescent (ECL) immunoassay based on the use of the MoOx QDs ECL probe for cytokeratin 19 fragment 21-1 (CYFRA21-1).

Menilli, L., et al. (2021). "Graphene Oxide and Graphene Quantum Dots as Delivery Systems of Cationic Porphyrins: Photo-Antiproliferative Activity Evaluation towards T24 Human Bladder Cancer Cells." Pharmaceutics **13**(9).

The development of new photodynamic therapy (PDT) agents designed for bladder cancer (BC) treatments is of utmost importance to prevent its recurrence and progression towards more invasive forms. Here, three different porphyrinic photosensitizers (PS) (TMPyP, Zn-TMPyP, and P1-C5) were non-covalently loaded onto graphene oxide (GO) or graphene quantum dots (GQDs) in a one-step process. The cytotoxic effects of the free PS and of the corresponding hybrids were compared upon blue (BL) and red-light (RL) exposure on T24 human BC cells. In addition, intracellular reactive oxygen species (ROS) and singlet oxygen generation were measured. TMPyP and Zn-TMPyP showed higher efficiency under BL (IC50: 0.42 and 0.22 mum, respectively), while P1-C5 was more active under RL (IC50: 0.14 mum). In general, these PS could induce apoptotic cell death through lysosomes damage. The in vitro photosensitizing activity of the PS was not compromised after their immobilization onto graphene-based nanomaterials, with Zn-TMPyP@GQDs being the most promising hybrid system under RL (IC50: 0.37 mug/mL). Overall, our data confirm that GO and GQDs may represent valid platforms for PS delivery, without altering their performance for PDT on BC cells.

Merlin, N. M., et al. (2019). "The effects of quantum psychological relaxation technique on self-acceptance in patients with breast cancer." Can Oncol Nurs J **29**(4): 232-236.

BACKGROUND: Psychological, as well as physical effects of a disease, and side effects of medications can influence the self-acceptance of patients. Low self-acceptance can lead patients to drop out of their therapy schedule and return to the hospital several months later in much worse condition. This study aimed to investigate the effects of quantum psychological relaxation technique on self-acceptance in breast cancer patients. METHODS: This study used a pre-post quasi-experimental design with a control group. The sample included 64 respondents selected using a consecutive sampling technique and divided into two groups: intervention group (n=32) and control group (n=32). The quantum psychological relaxation technique was administered in two phases with three sessions for each phase. Six sessions were estimated at 90-120 minutes and 15-20 minutes for each. The data on patients' self-acceptance were collected using the Acceptance of Illness Scale (AIS) questionnaire and were statistically analyzed using t-test and Wilcoxon test. RESULTS: Self-acceptance in the intervention group increased after being given the intervention with a p-value <0.001. However, in the control group there was no significant increase in self-acceptance with a p-value >0.005. CONCLUSIONS: The quantum psychological relaxation technique had an effect on the self-acceptance of breast cancer patients. RECOMMENDATION: Further studies of the effects of quantum psychological relaxation technique on depression and life quality of patients need to be conducted.

Miyashita, M., et al. (2016). "Quantitative diagnosis of HER2 protein expressing breast cancer by single-particle quantum dot imaging." Cancer Med **5**(10): 2813-2824.

Overexpression of HER2 is one of the major causes of breast cancer, and therefore precise diagnosis of its protein expression level is important. However, current methods estimating the HER2-expression level are insufficient due to problem with the lack of quantification. This might result in a gap between diagnostics and therapeutics targeting HER2. Therefore, a new effective diagnostic method is needed. We developed a new immunohistochemical (IHC) technique with quantum dots (QD)-conjugated trastuzumab using single-particle imaging to quantitatively measure the HER2 expression level. Tissues from 37 breast cancer patients with available detailed clinical information were tested by IHC with QDs (IHC-QD) and the correlation with IHC with 3,3'-diaminobenzidine (DAB), fluorescence in situ hybridization (FISH), and IHC-QD was examined. The number of QD-conjugated trastuzumab particles binding specifically to a cancer cell was precisely calculated as the IHC-QD score. The IHC-QD score in 37 cases was correlated proportionally with the score of HER2 gene copy number as assessed by FISH (R = 0.83). When HER2 positivity was judged to be positive, the IHC-QD score with our cut-off level was exactly concordant with the FISH score with a cut-off value of 2.0. Furthermore, IHC-QDs score and time to progression (TTP) of trastuzumab therapy were well correlated in HER2-positive cases (R = 0.69). Conversely, the correlation between FISH score and TTP was not observed. We developed a precisely quantitative IHC method using trastuzumab-conjugated QDs and single-particle imaging analysis and propose the possibility of using IHC-QDs score as a predictive factor for trastuzumab therapy.

Moasses Ghafary, S., et al. (2022). "Design and preparation of a theranostic peptideticle for targeted cancer therapy: Peptide-based codelivery of doxorubicin/curcumin and graphene quantum dots." Nanomedicine **42**: 102544.

Although chemotherapy has been known as a powerful medication for cancer treatment over the years,

there is an important necessity for designing a novel targeted drug delivery system to overcome the drawbacks of this conventional method including undesired side effects on normal cells and drug resistance. The structural differences between the surface of cancerous and normal cells allow to design and engineer targeted drug delivery systems for cancer treatment. Integrins as one of the cell surface receptors over-expressed in cancer cells could potentially be suitable candidates for targeting cancer cells. In the present study, the novel nano-carriers based on designed MiRGD peptides and graphene quantum dots (GQDs) have been used for targeted delivery of doxorubicin (Dox) and curcumin (Cur) as hydrophilic and hydrophobic drug models, respectively. The prepared nano-composites were characterized by UV-vis and photoluminescence (PL) spectroscopies, Zeta-Sizer and transmission electron microscopy (TEM). Altogether, the results of cellular uptake and fluorimetric assays performed in HUVEC and HFF cells as models of alphav integrin-over-expressed cancer and normal cells, respectively, besides in-vivo study on breast cancer bearing BALB/c mice, demonstrated that the prepared nano-composites can be considered as suitable multifunctional theranostic peptideticles for targeted drug delivery and tracking.

Moazampour, M., et al. (2021). "Femtomolar determination of an ovarian cancer biomarker (miR-200a) in blood plasma using a label free electrochemical biosensor based on L-cysteine functionalized ZnS quantum dots." Anal Methods **13**(17): 2021-2029.

In the present study, a label-free electrochemical genosensor was designed based on ZnS quantum dots functionalized with l-cysteine (Cys-ZnS-QDs) to detect miR-200a, as a special ovarian cancer biomarker. The Cys-ZnS-QD genosensor was characterized by transmission electron microscopy (TEM), UV-Vis absorption and fluorescence methods. Cys-ZnS-QDs are electrodeposited on the glassy carbon electrode surface and act as a suitable substrate for immobilization of the DNA probe. The effective parameters in the preparation of the genosensor are optimized to improve its analytical performance. The analytical performance of the genosensor has been investigated using electrochemical impedance spectroscopy. Under optimal conditions, the linear range and the detection limit of miR-200a were found to be 1.0 x 10-14 to 1.0 x 10-6 M and 8.4 fM. In addition, the genosensor is used to detect the target complementary miRNA strand from a single-base mismatch miRNA strand. Finally, this label-free electrochemical biosensor was used to detect miR-200a in human plasma without using any amplification method.

Mognetti, B., et al. (2010). "Preferential killing of cancer cells using silicon carbide quantum dots." J Nanosci Nanotechnol **10**(12): 7971-7975.

Silicon carbide quantum dots are highly luminescent biocompatible nanoparticles whose properties might be of particular interest for biomedical applications. In this study we investigated Silicon Carbide Quantum Dots (3C-SiC QDs) cellular localisation and influence on viability and proliferation on oral squamous carcinoma (AT-84 and HSC) and immortalized cell lines (S-G). They clearly localize into the nuclei, but the presence of 3C-SiC QDs in culture medium provoke morphological changes in cultured cells. We demonstrate that 3C-SiC QDs display dose- and time-dependent selective cytotoxicity on cancer versus immortalized cells in vitro. Since one of the limitations of classical antineoplastic drugs is their lack of selectivity, these results open a new way in the search for antiproliferative drugs.

Mohammad, S. N. (1985). "A quantum mechanical approach to the theory of cancer from polynuclear compounds. Metabolic activation and carcinogenicity of extended anilines and aminoazo compounds." Mol Pharmacol **27**(1): 148-155.

Calculations have been carried out of the electronic structure and molecular properties in relation to metabolic activation and carcinogenic activities of polycyclic aromatic amines (PAAs). Quantum mechanical molecular orbital method MINDO/3 is employed in the calculations mainly on anilines, extended anilines, and aminoazo and other azo compounds. The calculations, in agreement with findings of Arcos and Argus, indicate that for the highest level of carcinogenic activity obtainable with the dicyclic aromatic amines, the amino substituent must be introduced at the terminal carbon atom of the longest conjugate chain. In the case of monocyclic compounds, in particular, charge distribution of the amino substitution aids in identifying the carcinogenic character of the PAAs. Our results demonstrate that ring hydroxylation leads to detoxification of the compounds. However, the major pathway leading to carcinogenic activity involves transformation to hydroxylamines and subsequently to electrophilic arylnitrenium ions (ANIs). These are in line with findings from experiments. Calculations of certain electronic parameters give expected relative carcinogenic potencies. In all cases the ANIs function as ambient electrophiles which can undergo both electrostatic and covalent binding with nucleophilic centers of proteins and DNA bases.

Mohammadi, R., et al. (2022). "Fluorescence sensing and imaging with carbon-based quantum dots for early diagnosis of cancer: A review." J Pharm Biomed Anal **212**: 114628.

This review discusses recent advances and the reported strategies over the last ten years on the use of carbon-based quantum dots (QDs), including carbon dots (CDs), graphene quantum dots (GQDs), and polymer dots (PDs) in the design of fluorescence imaging and biosensing system for early diagnosis of cancers. Besides, this study comprehensively reports the latest developments in these years in the fluorescence imaging (FI) area with special attention to carbon-based QDs that take advantage of the excellent properties offered by these zero-dimensional (0D) nanomaterials as fluorescent tags. The most remarkable advantages of these carbon nanomaterials in the development of fluorescence sensing and imaging strategies compared to the conventional dyes arise from sharp emission spectra, long photostability, low-cost synthesis, reliability, reproducibility, high fluorescent intensity, and high surface functional groups such as carboxyl and amide, which impart better solubility in many solvents and aqueous media and facilitate their easy functionalization with biological species. The final section discusses the main challenges to be met to take full advantage of these properties in fluorescence bio-sensing and imaging as well as the possible future trends in this field based on the great advances that have occurred in recent years.

Monroe, J. D., et al. (2019). "Anticancer Photodynamic Therapy Properties of Sulfur-Doped Graphene Quantum Dot and Methylene Blue Preparations in MCF-7 Breast Cancer Cell Culture." Photochem Photobiol **95**(6): 1473-1481.

Photodynamic therapy (PDT) is a field with many applications including chemotherapy. Graphene quantum dots (GQDs) exhibit a variety of unique properties and can be used in PDT to generate singlet oxygen that destroys pathogenic bacteria and cancer cells. The PDT agent, methylene blue (MB), like GQDs, has been successfully exploited to destroy bacteria and cancer cells by increasing reactive oxygen species generation. Recently, combinations of GQDs and MB have been shown to destroy pathogenic bacteria via increased singlet oxygen generation. Here, we performed a spectrophotometric assay to detect and measure the uptake of GQDs, MB and several GQD-MB combinations in MCF-7 breast cancer cells. Then, we used a cell counting method to evaluate the cytotoxicity of GQDs, MB and a 1:1 GQD:MB preparation. Singlet oxygen generation in cells was then detected and measured using singlet oxygen sensor green. The dye, H2 DCFDA, was used to measure reactive oxygen species production. We found that GQD and MB uptake into MCF-7 cells occurred, but that MB, followed by 1:1 GQD:MB, caused superior cytotoxicity and singlet oxygen and reactive oxygen species generation. Our results suggest that methylene blue's effect against MCF-7 cells is not potentiated by GQDs, either in light or dark conditions.

Monteiro, C. A. P., et al. (2020). "Evaluating internalization and recycling of folate receptors in breast cancer cells using quantum dots." J Photochem Photobiol B **209**: 111918.

Folic acid (FA) regulates metabolic activities essential to the human body. FA receptor (FR) overexpression has been reported for many cancers, but there are still few or conflicting data about FRs in breast cancer cells. Quantum dots (QDs) have arisen as tools to elucidate aspects on FRs, due to their unique physicochemical properties. Herein, QDs conjugated to FA were explored to study the internalization and recycling of FRs in breast cancer cells, using HeLa as an out-group control. QDs were covalently conjugated to FA under different conditions. The best conjugate was applied to study FRs in HeLa, MCF7, MDA-MB231, and T47D cells applying confocal microscopy and flow cytometry analyses. The conjugation efficiency and specificity were evaluated, respectively, using fluorescence correlation spectroscopy (FCS) and saturation assays. FCS confirmed the effectiveness of the conjugation. HeLa and T47D had/internalized a higher amount of FRs (95% and 90% of labeling, respectively) than MDA-MB231 cells (68%). MCF7 cells seem to have very low functional FRs (3%). Saturation assays proved the specificity of QD-FA conjugates and suggested that FR recycling rate is low in the majority of cells studied, except for T47D. QD-FA conjugates were successfully developed. Therapies targeting FRs may be more effective for HeLa, T47D, and MDA-MB231.

Moradi-Kalbolandi, S., et al. (2020). "Development of an anti-CD45RA-quantum dots conjugated scFv to detect leukemic cancer stem cells." Mol Biol Rep **47**(1): 225-234.

Leukemic cancer stem cells (LSCs), aberrantly overexpressing CD45RA are among the major causes of relapse following chemotherapy in patients with acute myeloid leukemia and serve as a highly sensitive marker for predicting relapse occurrence following chemotherapy. The main purpose of current study was to develop a sensitive approach for detecting LSCs based on a conjugate of an anti-CD45 scFv and quantum dot. The variable light and heavy chain sequences of a recently developed anti-CD45RA monoclonal antibody were derived from hybridoma cells and PCR amplified to construct scFv. Following insertion of scFv gene into a pET32a-lic vector and expression in Escherichia coli and purification, the purified scFv, was conjugated with carbon dots (C dots) and used for the detection of CD45RA (+)cells while CD45RA-cells served as negative control. Subsequently, Functional activity of

the conjugate was analyzed by flow cytometry and ICC to detect the cell surface antigen binding and detection ability. Based on results, purified CD45RA scFv conjugated C dots could specifically recognize CD45RA positive cells, but not any CD45RA negative ones. In conclusion, here we developed a low-cost but very efficient approach for detection of CD45RA positive cells including LSCs.

Morosini, V., et al. (2011). "Quantum dot-folic acid conjugates as potential photosensitizers in photodynamic therapy of cancer." Photochem Photobiol Sci **10**(5): 842-851.

This study examined the in vitro potential of bioconjugated quantum dots (QDs) as photosensitizers for photodynamic therapy (PDT). According to our previous approaches using photosensitizers, folic acid appears to be an optimal targeting ligand for selective delivery of attached therapeutic agents to cancer tissues. We synthesized hydrophilic near infrared emitting CdTe(S)-type QDs conjugated with folic acid using different spacers. Photodynamic efficiency of QDs conjugated or not with folic acid was evaluated on KB cells, acting as a positive control due to their overexpression of FR-alpha, and HT-29 cells lacking FR-alpha, as negative control. A design of experiments was suggested as a rational solution to evaluate the impacts of each experimental factor (QD type and concentration, light fluence and excitation wavelength, time of contact before irradiation and cell phenotype). We demonstrated that, for concentrations lower than 10 nM, QDs displayed practically no cytotoxic effect without light exposure for both cell lines. Whereas QDs at 2.1 nM displayed a weak photodynamic activity, a concentration of 8 nM significantly enhanced the photodynamic efficiency characterized by a light dose-dependent response. A statistically significant difference in photodynamic efficiency between KB and HT-29 cells was evidenced in the case of folic acid-conjugated QDs. Optimal conditions led to an enhanced photocytotoxicity response, allowing us to validate the ability of QDs to generate a photodynamic effect and of folic acid-conjugated QDs for targeted PDT.

Naderi, S., et al. (2018). "Cadmium telluride quantum dots induce apoptosis in human breast cancer cell lines." Toxicol Ind Health **34**(5): 339-352.

INTRODUCTION: Semiconductor quantum dots (QDs), especially those containing cadmium, have undergone marked improvements and are now widely used nanomaterials in applicable biological fields. However, great concerns exist regarding their toxicity in biomedical applications. Because of the lack of sufficient data regarding the toxicity mechanism of QDs, this study aimed to evaluate the cytotoxicity of three types of QDs: CdTe QDs, high yield CdTe QDs, and CdTe/CdS core/shell QDs on two human breast cancer cell lines MDA-MB468 and MCF-7. METHODS: The breast cancer cells were treated with different concentrations of QDs, and cell viability was evaluated via MTT assay. Hoechst staining was applied for observation of morphological changes due to apoptosis. Apoptotic DNA fragmentation was visualized by the agarose gel electrophoresis assay. Flow cytometric annexin V/propidium iodide (PI) measurement was used for apoptosis detection. RESULTS: A significant decrease in cell viability was observed after QDs treatment ($p < 0.05$). Apoptotic bodies and chromatin condensation was observed by Hoechst staining. DNA fragmentation assay demonstrated a DNA ladder profile in the exposed cells and also annexin V/PI flow cytometry confirmed apoptosis in a dose-dependent manner. CONCLUSION: Our results revealed that CdTe, high yield CdTe, and CdTe/CdS core/shell QDs induce apoptosis in breast cancer cell lines in a dose-dependent manner. This study would help realizing the underlying cytotoxicity mechanism, at least partly, of CdTe QDs and may provide information for the development of nanotoxicology and safe use of biological applications of QDs.

Nafiujjaman, M., et al. (2018). "Synthesis of Nitrogen- and Chlorine-Doped Graphene Quantum Dots for Cancer Cell Imaging." J Nanosci Nanotechnol **18**(6): 3793-3799.

In this study, we synthesized high quantum yield nitrogen and chlorine-doped graphene quantum dots (Cl-GQDs-N) for cancer cell imaging using simple and high production yield hydrothermal method from low-cost fructose. Prepared Cl-GQDs-N are about 30 nm in diameter and these Cl-GQDs-N display powerful blue color photoluminescence under the 365 nm UV lamp. We have further investigated their optical performances under various conditions. In vitro study shows no toxicity effect in normal and cancer cells treated with Cl-GQDs-N. Finally, we believe that our synthesized Cl-GQDs-N will bring more application opportunities in the field of bioimaging, optoelectronics and beyond.

Naik, K., et al. (2022). "A Strategic Review on Carbon Quantum Dots for Cancer-Diagnostics and Treatment." Front Bioeng Biotechnol **10**: 882100.

The understanding of the genesis of life-threatening cancer and its invasion calls for urgent development of novel technologies for real-time observations, early diagnosis, and treatment. Quantum dots (QDs) grabbed the spotlight in oncology owing to their excellent photostability, bright fluorescence, high biocompatibility, good electrical and chemical stability with minimum invasiveness. Recently, carbon QDs (CQDs) have become popular over toxic inorganic QDs

in the area of bioimaging, biosensing, and drug delivery. Further, CQDs derived from natural sources like biomolecules and medicinal plants have drawn attention because of their one-pot, low-cost and ease of synthesis, along with remarkable tunable optical properties and biocompatibility. This review introduces the synthesis and properties of CQDs derived from natural sources, focusing on the applicability of CQD-based technologies as nano-theranostics for the diagnosis and treatment of cancer. Furthermore, the current issues and future directions for the transformation of CQDs-based nanotechnologies to clinical applications are highlighted.

Natmai, S., et al. (2022). "The aggregation of multiple miR-29a cancer biomarkers induced by graphene quantum dots: Molecular dynamics simulations." J Mol Graph Model **116**: 108267.

MicroRNAs (miRNAs) are small non-coding RNAs that play a role in regulating gene expression. MiRNAs are focused on as potential cancer biomarkers due to their involvement in the cancer development. New effective techniques for extracting miRNA from a biological matrix is important. Recently, graphene quantum dots (GQDs) have been used to detect DNA/RNA in many sensor platforms, but the application in miRNA extraction remains limited. To extract miRNAs, the miRNA adsorption and desorption on GQD are the key. Thus, in this work, the adsorption mechanism of excess miRNA on GQD in solution is revealed using Molecular dynamics simulations. The miRNA assemblies on one and two GQDs were studied to explore the possibility of using GQD for miRNA extraction. The folded miR-29a molecule, one of key cancer biomarkers, is used as an miRNA model. Three systems with one (6miR) and two GQDs (with parallel (6miR_2GP) and sandwich (6miR_2GS) organisations) in six-miR-29a solution were set. The data show excess miR-29a can reduce the miR-29a-GQD binding efficiency. The opening of intrabase pairing of GQD-absorbed miR-29a facilitates the interbase coupling resulting in the self-aggregation of miR-29a. The GQD organisation also affects the miR-29a adsorption ability. The additional GQDs result in the tighter miR-29a adsorption which can retard the miR-29a desorption. The proper GQD concentration is thus important to successfully collect all miR-29a and accommodate the easy miR-29a dissociation. Our results can be useful for a design of DNA probe and choosing decent nanosized GRA concentration for experimental setups.

Ncapayi, V., et al. (2021). "Diagnosis of Prostate Cancer and Prostatitis Using near Infra-Red Fluorescent AgInSe/ZnS Quantum Dots." Int J Mol Sci **22**(22).

The link between the microbiome and cancer has led researchers to search for a potential probe for intracellular targeting of bacteria and cancer. Herein, we developed near infrared-emitting ternary AgInSe/ZnS quantum dots (QDs) for dual bacterial and cancer imaging. Briefly, water-soluble AgInSe/ZnS QDs were synthesized in a commercial kitchen pressure cooker. The as-synthesized QDs exhibited a spherical shape with a particle diameter of 4.5 +/- 0.5 nm, and they were brightly fluorescent with a photoluminescence maximum at 705 nm. The QDs showed low toxicity against mouse mammary carcinoma (FM3A-Luc), mouse colon carcinoma (C26), malignant fibrous histiocytoma-like (KM-Luc/GFP) and prostate cancer cells, a greater number of accumulations in Staphylococcus aureus, and good cellular uptake in prostate cancer cells. This work is an excellent step towards using ternary QDs for diagnostic and guided therapy for prostate cancer.

Nene, L. C. and T. Nyokong (2021). "Photo-sonodynamic combination activity of cationic morpholino-phthalocyanines conjugated to nitrogen and nitrogen-sulfur doped graphene quantum dots against MCF-7 breast cancer cell line in vitro." Photodiagnosis Photodyn Ther **36**: 102573.

In this work, we explore the reactive oxygen species (ROS) generation abilities of cationic morpholino-substituted-phthalocyanine (Pc) conjugated to nitrogen (NGQDs) and nitrogen-sulfur (NSGQDs) doped-graphene quantum dots upon irradiation with light for photodynamic therapy (PDT), ultrasound for sonodynamic therapy (SDT) and the combination of both in photo-sonodynamic therapy (PSDT). The in vitro cytotoxicity studies were conducted using the Michigan Cancer Foundation-7 breast cancer cell lines (MCF-7 cells). For PDT treatments, only the (1)O2 was detected for all the sensitizers, whereas both the (1)O2 and (*)OH radicals were evident after SDT and PSDT treatments. An increase in the (1)O2 generation was observed for the conjugates compared to the GQDs and the Pc alone. However, the (*)OH radicals were reduced in the conjugates compared to the GQDs and the Pc alone. The NGQDs generally showed better ROS generation efficacy compared to the NSGQDs, alone and in the conjugates. The combination therapy also shows improved efficacy compared to the monotherapies for the Pcs and Pc-GQDs conjugates.

Nie, Y., et al. (2021). "MXene-Derived Quantum Dot@Gold Nanobones Heterostructure-Based Electrochemiluminescence Sensor for Triple-Negative Breast Cancer Diagnosis." Anal Chem **93**(51): 17086-17093.

MXene material has been gradually studied in recent years due to its fascinating characteristics. This work developed a novel MXene-derived quantum dots (MQDs) @gold nanobones (Au NBs) heterostructure as

the electrochemiluminescence (ECL) sensor. First, MXene and MQDs were synthesized via the green preparation process, which avoided the harm of hydrofluoric acid to humans and the environment. There was a strong ECL signal enhancement in the MQD@Au NBs heterostructure. On the one hand, Au NBs with surface plasmon resonance (SPR) effect acted as an "electronic regulator" that can transfer electrons to itself to control over-injection of electrons into the conduction band of MQDs. The luminous signal of MQDs can be efficiently generated and significantly amplified in the ECL sensing process. On the other hand, the work function of MQDs with excellent conductivity was relatively close to that of Au NBs in the heterostructure. So, ECL quenching caused by short-distance electron transfer between luminophore and Au nanomaterial has been effectively suppressed. The MQD@Au NBs heterostructure-based ECL sensing system was applied to determine miRNA-26a in the serum of patients with triple-negative breast cancer. It not only provides ideas for the green synthesis of MXene but also provides a guide for the application of MQD@Au NBs heterostructure in the field of ECL sensing.

Nifontova, G., et al. (2019). "Cancer Cell Targeting With Functionalized Quantum Dot-Encoded Polyelectrolyte Microcapsules." Front Chem **7**: 34.

Imaging agents and drug carriers are commonly targeted toward cancer cell through functionalization with specific recognition molecules. Quantum dots (QDs) are fluorescent semiconductor nanocrystals whose extraordinary brightness and photostability make them attractive for direct fluorescent labeling of biomolecules or optical encoding of the membranes and cells. Here, we analyse the cytotoxicity of QD-encoded microcapsules, validate an approach to the activation of the microcapsule's surface for further functionalization with monoclonal antibody Trastuzumab, a humanized monoclonal antibody targeting the extracellular domain of the human epidermal growth factor receptor 2 (HER2) and already in clinical use for the treatment of HER2 positive breast cancer. In addition, we characterize the cell-specific targeting activity of the resultant bio-conjugate by immunofluorescence assay (IFA) and real-time analysis of interaction of the conjugates with live HER2 overexpressing human breast cancer cells. We demonstrate, that encapsulation of QDs into the polymer shell using the layer-by-layer deposition method yields highly fluorescent polyelectrolyte microcapsules with a homogeneous size distribution and biocompatibility upon in vitro treatment of cancer cells. Carbodiimide surface activation ensures optimal disperse and optical characteristics of the QD-encoded microcapsules before antibody conjugation. The prepared conjugates of the microcapsules with cancer-specific monoclonal antibody targeting HER2 provide sufficiently sensitive and specific antibody-mediated binding of the microcapsules with live cancer cells, which demonstrated their potential as prospective cancer cell-targeting agents.

Nigam Joshi, P., et al. (2017). "Multifunctional inulin tethered silver-graphene quantum dots nanotheranostic module for pancreatic cancer therapy." Mater Sci Eng C Mater Biol Appl **78**: 1203-1211.

Cancer nanotechnology is an emerging area of cancer diagnosis and therapy. Although considerable progress has been made for targeted drug delivery systems to deliver anticancer agents to particular site of interest, new nanomaterials are frequently being developed and explored for better drug delivery efficiency. In the present work, we have explored a novel nanoformulation based on silver-graphene quantum dots (Ag-GQDs) nanocomposite for its successful implementation for pancreatic cancer specific drug delivery in wistar rats. Carboxymethyl inulin (CMI); a modified variant of natural polysaccharide inulin is tethered with the nanocomposite via carbodiimide coupling to enhance the biocompatibility of nanoformulation. Experiments are performed to investigate the cytotoxicity reduction of silver nanoparticles after inulin tethering as well as anticancer efficacy of the system using 5-Fluorouracil (5-FU) as model drug. SEM, TEM, FT-IR, UV-vis, photoluminescence and anti proliferative assays (MTT) are performed for characterisation of the nanocomposite. Hyaluronic acid (HA) is conjugated as targeting moiety for CD-44 (cancer stem cell marker) to fabricate a complete targeted drug delivery vehicle specific for pancreatic cancer. In the present work two prime objectives were achieved; mitigation the toxicity of silver nanoparticles by inulin coating and it's in vivo application for pancreatic cancer.

Nigam, P., et al. (2014). "Graphene quantum dots conjugated albumin nanoparticles for targeted drug delivery and imaging of pancreatic cancer." J Mater Chem B **2**(21): 3190-3195.

Pancreatic cancer is considered to be the deadliest of all cancers due to its poor prognosis and resistance to conventional therapies. In this study, the potential of hyaluronic acid functionalized and green fluorescent graphene quantum dot (GQD)-labeled human serum albumin nanoparticles for pancreatic cancer specific drug delivery and bioimaging was explored. GQDs with tunable fluorescence properties and biocompatibility have attracted much more interest in recent years as compared to their metal semiconductor counterparts. We adopted lawsone (2-hydroxy-1,4-naphthoquinone) as a novel reducing agent for the synthesis of quantum dots and, in addition to excellent

fluorescence of the synthesized GQDs, a good quantum yield of approximately 14% was also obtained. Gemcitabine, the most preferred drug for pancreatic cancer treatment, was encapsulated in albumin nanoparticles, and it was observed that our nanoformulation significantly enhanced the bioavailability and sustained release property of the drug to pancreatic cancer cells in vitro. Moreover, the GQD-mediated bioimaging was excellent and enhanced the efficacy of our system as a drug delivery vehicle.

Olerile, L. D. (2020). "Further Development of Near-Infrared Mediated Quantum Dots and Paclitaxel Co-loaded Nanostructured Lipid Carrier System for Cancer Theragnostic." Technol Cancer Res Treat **19**: 1533033820914308.

Of colloidal systems, ceteris paribus, nanostructured lipid carriers are second to none in offering a single-unit platform for multifunctional benefits. Quantum dots are known to possess unique properties that make them ideal for imaging purpose and that they may be used for cancer detection. For several decades, paclitaxel has been the most effective drug against a wide range of solid tumours. Theragnostic nanomedicine provides a platform to monitor, evaluate, and individualize treatment in real time. Evaluation of cancer treatment outcome at an early stage therapy is key to increase survival prospects of a patient. Previously, a novel co-loaded nanostructured lipid carriers' theragnostic system for parenteral administration was developed. The aim of this study was to further investigate the co-loaded nanostructured lipid carriers in order to provide interpretation necessary for preclinical elucidation of the formulation, in part. The co-loaded nanostructured lipid carriers were prepared by oil/water emulsification-solvent evaporation technique. In this study, stability and co-loaded nanostructured lipid carriers' internalization by MCF 7 and HepG2 cells were investigated. The co-loaded nanostructured lipid carriers was stable at 4 degrees C for 1 month. The formulation was successfully internalized by MCF-7 and HepG2 cells. Nevertheless, the co-loaded nanostructured lipid carrier was more apt for MCF-7 cells. This finding affirms the formulation to be the most appropriate for breast cancer treatment. In addition, if taken correctly by a patient for a month, the formulation would give true reflection of the contents' amounts, the factor paramount to appropriate changes in treatment protocol. It can therefore safely be concluded that the co-loaded nanostructured lipid carrier formulation may be potentially an effective theragnostic translational system.

Olerile, L. D., et al. (2017). "Near-infrared mediated quantum dots and paclitaxel co-loaded nanostructured lipid carriers for cancer theragnostic." Colloids Surf B Biointerfaces **150**: 121-130.

Timing is an important factor in cancer management. Theragnostic systems have benefit of improving patients' life-quality by expediting therapeutic decisions. The objective of this study was to explore the potential of co-loaded [quantum dots (CdTe/CdS/ZnS) and paclitaxel] NLC (nanostructured lipid carriers) as a parenteral multifunctional delivery system. The co-loaded NLC was prepared by emulsion-evaporation and low temperature-solidification method utilising glyceryl monostearate, oleic acid, and soya phosphatidylcholine as lipid matrix. In characterising the co-loaded NLC, physicochemical properties of particle size, polydispersity index (PDI), zeta potential (ZP), morphology, encapsulation efficacy (EE) and drug loading (DL) were investigated. Moreover, in-vitro paclitaxel release profile, cytotoxicity, histopathological, in-vivo anti-tumour efficacy, and in-vivo and ex-vivo fluorescence optical imaging abilities of the co-loaded NLC were assessed. The mean particle size, PDI and ZP were reported to be 115.93+/-1.61nm, 0.17+/-0.04 and -0.22+/-0.03mV, respectively. The particles were spheroid-like in shape with relatively smooth surface. A higher EE (80.70+/-2.11%) and DL (4.68+/-0.04%) were recorded. The coloaded NLC exhibited a biphasic pattern of drug release. IC50 value was found to be 1.05+/-0.58muM. The tumour growth inhibition rate of 77.85% was registered. The in-vivo and ex-vivo imaging results indicated capability of the co-loaded NLC to specifically target and detect the H22 tumour. Tissues showed no significant cytoarchitectural differences. We can satisfactorily conclude that co-loaded NLC formulation can be qualified as a splendid parenteral drug delivery system foundation for cancer theragnostic.

Omer, W. E., et al. (2021). "Cancer antigen 125 assessment using carbon quantum dots for optical biosensing for the early diagnosis of ovarian cancer." RSC Adv **11**(49): 31047-31057.

Fluorometric quantification of biological molecules is a key feature used in many biosensing studies. Fluorescence resonance energy transfer (FRET) using highly fluorescent quantum dots offers highly sensitive detection of the in-proximity wide variety of analyst molecules. In this contribution, we report the use of carbon quantum dots (CDs) for the ultrasensitive optical biosensing of cancer antigen 125 (CA-125) in the early malignant stage. This approach is based on monitoring the quenching of CDs luminescence at 535 nm by CA-125 after excitation at 425 nm and pH 10. The calibration of this method was performed in the concentration range of CA-125 from 0.01 to 129 U ml(-1) (R (2) = 0.99) with a detection limit of 0.66 U ml(-1), which matches remarkably with the standard

chemiluminometric method in control and real patient samples. The sensing mechanism for cancer antigen 125 assessment was discussed on the basis of fluorescence quenching of CDs and time-resolved photoluminescence spectroscopy. The current method is easy, sensitive, cost-effective and provides a wide range of validity, which helps in overcoming the limitations of high cost and time consumption exhibited by many other traditional clinical assays for CA-125 quantification.

Onoshima, D., et al. (2015). "Multifunctional quantum dots-based cancer diagnostics and stem cell therapeutics for regenerative medicine." Adv Drug Deliv Rev **95**: 2-14.

A field of recent diagnostics and therapeutics has been advanced with quantum dots (QDs). QDs have developed into new formats of biomolecular sensing to push the limits of detection in biology and medicine. QDs can be also utilized as bio-probes or labels for biological imaging of living cells and tissues. More recently, QDs has been demonstrated to construct a multifunctional nanoplatform, where the QDs serve not only as an imaging agent, but also a nanoscaffold for diagnostic and therapeutic modalities. This review highlights the promising applications of multi-functionalized QDs as advanced nanosensors for diagnosing cancer and as innovative fluorescence probes for in vitro or in vivo stem cell imaging in regenerative medicine.

Orndorff, R. L. and S. J. Rosenthal (2009). "Neurotoxin quantum dot conjugates detect endogenous targets expressed in live cancer cells." Nano Lett **9**(7): 2589-2599.

High affinity peptide neurotoxins are effective agents for integrating technological advances with biological inquiries. Both chlorotoxin (CTX) and dendrotoxin-1 (DTX-1) are peptide neurotoxins demonstrated to bind targets expressed by glioma cancer cells and are suitable ligands for quantum dot (QD) live cell investigations. Here, we present dual labeling of endogenously expressed cellular proteins within living cells utilizing high affinity peptide neurotoxins conjugated to QDs. Multiplexing experiments reveal quantifiable evidence that CTX and DTX-1 conjugated QDs may potentially be used as a live assessment of markers toward identification of cancer cell presence.

Ortega, G. A., et al. (2021). "Rodlike Particles of Polydopamine-CdTe Quantum Dots: An Actuator As a Photothermal Agent and Reactive Oxygen Species-Generating Nanoplatform for Cancer Therapy." ACS Appl Mater Interfaces **13**(36): 42357-42369.

Herein, novel rodlike CdTe@MPA-PDA particles based on polydopamine (PDA) loaded with CdTe quantum dots (QDs) capped with mercaptopropionic acid (CdTe@MPA QDs) with atypical chemical features are evaluated as a potential actuator for photothermal therapy and oxidative stress induction. Under mild conditions established for the safe and efficient use of lasers, temperature increases of 10.2 and 7.8 degrees C, photothermal conversion efficiencies of 37.7 and 26.2%, and specific absorption rates of 99 and 69 W/g were obtained for CdTe@MPA-PDA and traditional PDA particles in water, respectively. The particles were set to interact with the human breast adenocarcinoma cell line MDA-MB-231. A significant cellular uptake with the majority of particles colocalized into the lysosomes was obtained at a concentration of 100 mug/mL after 24 h. Additionally, CdTe@MPA-PDA and CdTe@MPA QDs showed significantly different internalization levels and loading kinetics profiles. For the first time, the thermal lens technique was used to demonstrate the stability of particle-like CdTe@MPA-PDA after heating at pH 7 and their migration within the heating region due to the thermodiffusion effect. However, under acidic pH-type lysosomes, a performance decrease in heating was observed, and the chemical feature of the particles was damaged as well. Besides, the internalized rodlike CdTe@MPA-PDA notably enhanced the induction of oxidative stress compared with PDA alone and CdTe@MPA QDs in MDA-MB-231 cells initiating apoptosis. Combining these effects suggests that after meticulous optimizations of the conditions, the CdTe@MPA-PDA particles could be used as a photothermal agent under mild conditions and short incubation time, allowing cytoplasmatic subcellular localization. On the other hand, the same particles act as cell killers by triggering reactive oxygen species after a longer incubation time and lysosomal subcellular localization due to the pH effect on the chemical morphology features of the CdTe@MPA-PDA particles.

Ouyang, J., et al. (2019). "2D Monoelemental Germanene Quantum Dots: Synthesis as Robust Photothermal Agents for Photonic Cancer Nanomedicine." Angew Chem Int Ed Engl **58**(38): 13405-13410.

As a new family member of the emerging two-dimensional (2D) monoelemental materials (Xenes), germanene has shown promising advantages over the prototypical 2D Xenes, such as black phosphorus (BP) and graphene. However, efficient manufacture of novel germanene nanostructures is still a challenge. Herein, a simple top-down approach for the liquid-exfoliation of ultra-small germanene quantum dots (GeQDs) is presented. The prepared GeQDs possess an average lateral size of about 4.5 nm and thickness of about 2.2 nm. The functionalized GeQDs were demonstrated to be robust photothermal agents (PTAs) with outstanding photothermal conversion efficacy (higher than those of

graphene and BPQDs), superior stability, and excellent biocompatibility. As a proof-of-principle, 2D GeQDs-based PTAs were used in fluorescence/photoacoustic/photothermal-imaging-guided hyperpyrexia ablation of tumors. This work could expand the application of 2D germanene to the field of photonic cancer nanomedicine.

Pan, J. and S. S. Feng (2009). "Targeting and imaging cancer cells by folate-decorated, quantum dots (QDs)-loaded nanoparticles of biodegradable polymers." Biomaterials **30**(6): 1176-1183.

We developed a new strategy to prepare folate-decorated nanoparticles of biodegradable polymers for Quantum dots (QDs) formulation for targeted and sustained imaging for cancer diagnosis at its early stage. Poly(lactide)-vitamin E TPGS (PLA-TPGS) copolymer and vitamin E TPGS-carboxyl (TPGS-COOH) copolymer were synthesized. Their blend at various weight ratio was used to prepare folate-decorated nanoparticles (NPs) for QDs formulation to improve their imaging effects and reduce their side effects. The TPGS-COOH on the NP surface was designed to conjugate folate-NH(2) with advantage to make the targeting effect adjustable. The size of such NPs was found in the range of 280-300nm. In vitro cellular uptakes of such NPs were investigated with confocal laser scanning microscopy (CLSM), which demonstrated much higher internalization of the folate-decorated QDs-loaded PLA-TPGS/TPGS-COOH NPs by MCF-7 breast cancer cells which are of over-expression of folate receptors than the cellular uptake by NIH 3T3 fibroblast cells which are of low expression of folate receptors. Compared with the free QDs, the QDs formulated in the PLA-TPGS/TPGS-COOH NPs showed lower in vitro cytotoxicity for both of MCF-7 cells and NIH 3T3 cells. Additionally, our findings indicated that under same conditions, cytotoxicity of QDs formulated in the PLA-TPGS/TPGS-COOH NPs is lower for normal cells such as NIH 3T3 cells than that for breast cancer such as MCF-7 breast cancer cells due to folate targeting effect. Targeted imaging by QDs formulated in folate-decorated PLA-TPGS/TPGS-COOH nanoparticles with better effects and less side effects is feasible.

Pan, Y., et al. (2017). "In vivo biodistribution and toxicity of intravesical administration of quantum dots for optical molecular imaging of bladder cancer." Sci Rep **7**(1): 9309.

Optical molecular imaging holds the potential to improve cancer diagnosis. Fluorescent nanoparticles such as quantum dots (QD) offer superior optical characteristics compared to organic dyes, but their in vivo application is limited by potential toxicity from systemic administration. Topical administration provides an attractive route for targeted nanoparticles with the possibility of minimizing exposure and reduced dose. Previously, we demonstrated successful ex vivo endoscopic imaging of human bladder cancer by topical (i.e. intravesical) administration of QD-conjugated anti-CD47. Herein we investigate in vivo biodistribution and toxicity of intravesically instilled free QD and anti-CD47-QD in mice. In vivo biodistribution of anti-CD47-QD was assessed with inductively coupled plasma mass spectrometry. Local and systemic toxicity was assessed using blood tests, organ weights, and histology. On average, there was no significant accumulation of QD outside of the bladder, although in some mice we detected extravesical biodistribution of QD suggesting a route for systemic exposure under some conditions. There were no indications of acute toxicity up to 7 days after instillation. Intravesical administration of targeted nanoparticles can reduce systemic exposure, but for clinical use, nanoparticles with established biosafety profiles should be used to decrease long-term toxicity in cases where systemic exposure occurs.

Pang, L., et al. (2014). "Characterization and cancer cell targeted imaging properties of human antivascular endothelial growth factor monoclonal antibody conjugated CdTe/ZnS quantum dots." Luminescence **29**(8): 1177-1182.

High luminescence quantum yield water-soluble CdTe/ZnS core/shell quantum dots (QDs) stabilized with thioglycolic acid were synthesized. QDs were chemically coupled to fully humanized antivascular endothelial growth factor165 monoclonal antibodies to produce fluorescent probes. These probes can be used to assay the biological affinity of the antibody. The properties of QDs conjugated to an antibody were characterized by ultraviolet and visible spectrophotometry, fluorescent spectrophotometry, sodium dodecyl sulfate-polyacrylamide gel electrophoresis, transmission electron microscopy and fluorescence microscopy. Cell-targeted imaging was performed in human breast cancer cell lines. The cytotoxicity of bare QDs and fluorescent probes was evaluated in the MCF-7 cells with an MTT viability assay. The results proved that CdTe/ZnS QD-monoclonal antibody nanoprobes had been successfully prepared with excellent spectral properties in target detections. Surface modification by ZnS shell could mitigate the cytotoxicity of cadmium-based QDs. The therapeutic effects of antivascular endothelial growth factor antibodies towards cultured human cancer cells were confirmed by MTT assay.

Pardo, J., et al. (2018). "Cancer Targeting and Drug Delivery Using Carbon-Based Quantum Dots and Nanotubes." Molecules **23**(2).

Currently cancer treatment is in large part non-specific with respect to treatment. Medication is often harsh on patients, whereby they suffer several undesired side effects as a result. Carbon-based nanoparticles have attracted attention in recent years due to their ability to act as a platform for the attachment of several drugs and/or ligands. Relatively simple models are often used in cancer research, wherein carbon nanoparticles are conjugated to a ligand that is specific to an overexpressed receptor for imaging and drug delivery in cancer treatment. These carbon nanoparticles confer unique properties to the imaging or delivery vehicle due to their nontoxic nature and their high fluorescence qualities. Chief among the ongoing research within carbon-based nanoparticles emerge carbon dots (C-dots) and carbon nanotubes (CNTs). In this review, the aforementioned carbon nanoparticles will be discussed in their use within doxorubicin and gemcitabine based drug delivery vehicles, as well as the ligand-mediated receptor specific targeted therapy. Further directions of research in current field are also discussed.

Park, Y., et al. (2014). "Spraying quantum dot conjugates in the colon of live animals enabled rapid and multiplex cancer diagnosis using endoscopy." ACS Nano **8**(9): 8896-8910.

The detection of colon cancer using endoscopy is widely used, but the interpretation of the diagnosis is based on the clinician's naked eye. This is subjective and can lead to false detection. Here we developed a rapid and accurate molecular fluorescence imaging technique using antibody-coated quantum dots (Ab-QDs) sprayed and washed simultaneously on colon tumor tissues inside live animals, subsequently excited and imaged by endoscopy. QDs were conjugated to matrix metalloproteinases (MMP) 9, MMP 14, or carcinoembryonic antigen (CEA) Abs with zwitterionic surface coating to reduce nonspecific bindings. The Ab-QD probes can diagnose tumors on sectioned mouse tissues, fresh mouse colons stained ex vivo and also in vivo as well as fresh human colon adenoma tissues in 30 min and can be imaged with a depth of 100 mum. The probes successfully detected not only cancers that are readily discernible by bare eyes but also hyperplasia and adenoma regions. Sum and cross signal operations provided postprocessed images that can show complementary information or regions of high priority. This multiplexed quantum dot, spray-and-wash, and endoscopy approach provides a significant advantage for detecting small or flat tumors that may be missed by conventional endoscopic examinations and bestows a strategy for the improvement of cancer diagnosis.

Peckys, D. B., et al. (2020). "Determining the Efficiency of Single Molecule Quantum Dot Labeling of HER2 in Breast Cancer Cells." Nano Lett **20**(11): 7948-7955.

Quantum dots exhibit unique properties compared to other fluorophores, such as bright fluorescence and lack of photobleaching, resulting in their widespread utilization as fluorescent protein labels in the life sciences. However, their application is restricted to relative quantifications due to lacking knowledge about the labeling efficiency. We here present a strategy for determining the labeling efficiency of quantum dot labeling of HER2 in overexpressing breast cancer cells. Correlative light- and liquid-phase electron microscopy of whole cells was used to convert fluorescence intensities into the underlying molecular densities of the quantum dots. The labeling procedure with small affinity proteins was optimized yielding a maximal labeling efficiency of 83%, which was applicable to the high amount of approximately 1.5 x 10(6) HER2 per cell. With the labeling efficiency known, it is now possible to derive the absolute protein expression levels in the plasma membrane and its variation within a cell and between cells.

Peng, C., et al. (2018). "Lysyl oxidase activates cancer stromal cells and promotes gastric cancer progression: quantum dot-based identification of biomarkers in cancer stromal cells." Int J Nanomedicine **13**: 161-174.

PURPOSE: Semiconductor quantum dots (QDs) are a promising alternative to organic fluorescent dyes for multiplexed molecular imaging of cancer stroma, which have great advantages in holistically analyzing the complex interactions among cancer stromal components in situ. PATIENTS AND METHODS: A QD probe-based multiplexed spectral molecular imaging method was established for simultaneous imaging. Three tissue microarrays (TMAs) including 184 gastric cancer (GC) tissues were constructed for the study. Multispectral analyses were performed for quantifying stromal biomarkers, such as lysyl oxidase (LOX). The stromal status including infiltrating of immune cells (high density of macrophages), angiogenesis (high density of microvessel density [MVD], low neovessel maturation) and extracellular matrix (ECM) remodeling (low density of type IV collagen, intense expression of matrix metalloproteinase 9 [MMP-9]) was evaluated. RESULTS: This study compared the imaging features of the QD probe-based single molecular imaging method, immunohistochemistry, and organic dye-based immunofluorescent methods, and showed the advantages of the QD probe-based multiple molecular imaging method for simultaneously visualizing complex components of cancer stroma. The risk of macrophages in high density, high MVD, low neomicrovessel maturation, MMP-9 expression and low type IV collagen was significantly increased for the expression of LOX. With the advantages of the established QD probe-based multiplexed molecular imaging method,

the spatial relationship between LOX and stromal essential events could be simultaneously evaluated histologically. Stromal activation was defined and then evaluated. Survival analysis showed that the stromal activation was correlated with overall survival and disease-free survival (P<0.001 for all). The expression of LOX was significantly increased in the intense activation subgroup (P<0.001). CONCLUSION: Quantifying assessment of the stroma indicates that the LOX may be a stromal marker for GC and stromal activation, which is not only responsible for the ECM remodeling morphologically, but also for the formation of invasive properties and recurrence. These results support the possibility to integrate morphological and molecular biomarker information for cancer research by the biomedical application of QDs.

Peng, C. W., et al. (2012). "Quantum-dots based simultaneous detection of multiple biomarkers of tumor stromal features to predict clinical outcomes in gastric cancer." Biomaterials **33**(23): 5742-5752.

Tumor microenvironment has been increasingly recognized as a complex and dynamic cancer society influencing tumor invasion and progression. The prognostic significance of this microenvironment is yet to be fully appreciated. A holistic approach to obtaining integrated information on key components in tumor microenvironment is essential. Here we reported on a quantum dots (QDs)-based simultaneous in-situ detection of infiltrating macrophages, tumor microvessels density (MVD) and neovessels maturity, in gastric cancer tissues, to obtain integrated information on these components, termed as combined tumor stromal features. These stromal features had the comparable prognostic value for overall survival, and even better prognostic value for disease-free survival, compared with traditional tumor cell-based clinico-pathological parameters. Subgroups of gastric cancer patients with favorable and unfavorable combined tumor stromal features were identified, with significantly different clinical outcomes. This study demonstrated the technical advantages of QDs-based simultaneous detection of multiple biomarkers in situ, revealed the important role of tumor stroma in cancer biology, and opened a new field to predict clinical outcome in gastric cancer from the perspectives of tumor microenvironment.

Pericleous, P., et al. (2012). "Quantum dots hold promise for early cancer imaging and detection." Int J Cancer **131**(3): 519-528.

Despite all major breakthroughs in recent years of research concerning the complex events that lead to cancer expression and metastasis, we are not yet able to effectively treat cancer that has spread to vital organs. The various clinical phases originating from cancer diagnosis through treatment and prognosis require a comprehensive understanding of these events, to utilise pre-symptomatic, minimally invasive and targeted cancer management techniques. Current imaging modalities such as ultrasound, computed tomography, magnetic resonance imaging and gamma scintigraphy facilitate the pre-operative study of tumours, but they have been rendered unable to visualise cancer in early stages, due to their intrinsic limitations. The semiconductor nanocrystal quantum dots (QDs) have excellent photo-physical properties, and the QDs-based probes have achieved encouraging developments in cellular (in vitro) and in vivo molecular imaging. However, the same unique physical and chemical properties which renowned QDs attractive may be associated with their potentially catastrophic effects on living cells and tissues. There are critical issues that need to be further examined to properly assess the risks associated with the manufacturing and use of QDs in cancer management. In this review, we aim to describe the current utilisation of QDs as well as their future prospective to decipher and confront cancer.

Perini, G., et al. (2022). "INSIDIA 2.0 High-Throughput Analysis of 3D Cancer Models: Multiparametric Quantification of Graphene Quantum Dots Photothermal Therapy for Glioblastoma and Pancreatic Cancer." Int J Mol Sci **23**(6).

Cancer spheroids are in vitro 3D models that became crucial in nanomaterials science thanks to the possibility of performing high throughput screening of nanoparticles and combined nanoparticle-drug therapies on in vitro models. However, most of the current spheroid analysis methods involve manual steps. This is a time-consuming process and is extremely liable to the variability of individual operators. For this reason, rapid, user-friendly, ready-to-use, high-throughput image analysis software is necessary. In this work, we report the INSIDIA 2.0 macro, which offers researchers high-throughput and high content quantitative analysis of in vitro 3D cancer cell spheroids and allows advanced parametrization of the expanding and invading cancer cellular mass. INSIDIA has been implemented to provide in-depth morphologic analysis and has been used for the analysis of the effect of graphene quantum dots photothermal therapy on glioblastoma (U87) and pancreatic cancer (PANC-1) spheroids. Thanks to INSIDIA 2.0 analysis, two types of effects have been observed: In U87 spheroids, death is accompanied by a decrease in area of the entire spheroid, with a decrease in entropy due to the generation of a high uniform density spheroid core. On the other hand, PANC-1 spheroids' death caused by nanoparticle photothermal disruption is accompanied with an overall increase in area and entropy due to the progressive loss of integrity and increase in variability of spheroid texture. We have

summarized these effects in a quantitative parameter of spheroid disruption demonstrating that INSIDIA 2.0 multiparametric analysis can be used to quantify cell death in a non-invasive, fast, and high-throughput fashion.

Phan, L. M. T., et al. (2018). "Synthesis of fluorescent silicon quantum dots for ultra-rapid and selective sensing of Cr(VI) ion and biomonitoring of cancer cells." Mater Sci Eng C Mater Biol Appl **93**: 429-436.

A facile one-step synthetic approach was developed for fabrication of fluorescent silicon quantum dots (Si QDs) and used as a probe for fluorescence detection of hexavalent chromium (Cr (VI)) in environmental water samples. The as-prepared Si QDs exhibit a strong fluorescence emission peak at 520nm with a quantum yield of 14.2%. The fluorescent Si QDs were rapidly produced by using ascorbic acid as a reductant at 55 degrees C. The emission peak of Si QDs at 420nm was effectively quenched upon the addition of Cr(VI). The Si QDs acted as the best fluorescent probe for the detection of Cr(VI) at PBS pH7.4. The developed probe possessed a good linear correlation (R(2)=0.992) between Cr(VI) concentration (1.25-40muM) and the (F0-F)/F0 values with a detection limit of 0.65muM. Furthermore, the Si QDs served as a bio-probe for fluorescence imaging of A549 lung cancer cells and cell viability results confirmed the good biocompatible nature of Si QDs. The as-fabricated Si QDs show several advantages such as rapidity, selectivity and biocompatibility for sensing of Cr(VI) and imaging of A549 cells, which opens a facile analytical platform for environmental and bioimaging applications.

Pietila, M., et al. (2013). "Mortalin antibody-conjugated quantum dot transfer from human mesenchymal stromal cells to breast cancer cells requires cell-cell interaction." Exp Cell Res **319**(18): 2770-2780.

The role of tumor stroma in regulation of breast cancer growth has been widely studied. However, the details on the type of heterocellular cross-talk between stromal and breast cancer cells (BCCs) are still poorly known. In the present study, in order to investigate the intercellular communication between human mesenchymal stromal cells (hMSCs) and breast cancer cells (BCCs, MDA-MB-231), we recruited cell-internalizing quantum dots (i-QD) generated by conjugation of cell-internalizing anti-mortalin antibody and quantum dots (QD). Co-culture of illuminated and color-coded hMSCs (QD655) and BCCs (QD585) revealed the intercellular transfer of QD655 signal from hMSCs to BCCs. The amount of QD double positive BCCs increased gradually within 48h of co-culture. We found prominent intercellular transfer of QD655 in hanging drop co-culture system and it was non-existent when hMSCs and BBCs cells were co-cultured in trans-well system lacking imminent cell-cell contact. Fluorescent and electron microscope analyses also supported that the direct cell-to-cell interactions may be required for the intercellular transfer of QD655 from hMSCs to BCCs. To the best of our knowledge, the study provides a first demonstration of transcellular crosstalk between stromal cells and BCCs that involve direct contact and may also include a transfer of mortalin, an anti-apoptotic and growth-promoting factor enriched in cancer cells.

Pilch, J., et al. (2021). "Quantum Dots as a Good Carriers of Unsymmetrical Bisacridines for Modulating Cellular Uptake and the Biological Response in Lung and Colon Cancer Cells." Nanomaterials (Basel) **11**(2).

Nanotechnology-based drug delivery provides a promising area for improving the efficacy of cancer treatments. Therefore, we investigate the potential of using quantum dots (QDs) as drug carriers for antitumor unsymmetrical bisacridine derivatives (UAs) to cancer cells. We examine the influence of QD-UA hybrids on the cellular uptake, internalization (Confocal Laser Scanning Microscope), and the biological response (flow cytometry and light microscopy) in lung H460 and colon HCT116 cancer cells. We show the time-dependent cellular uptake of QD-UA hybrids, which were more efficiently retained inside the cells compared to UAs alone, especially in H460 cells, which could be due to multiple endocytosis pathways. In contrast, in HCT116 cells, the hybrids were taken up only by one endocytosis mechanism. Both UAs and their hybrids induced apoptosis in H460 and HCT116 cells (to a greater extent in H460). Cells which did not die underwent senescence more efficiently following QDs-UAs treatment, compared to UAs alone. Cellular senescence was not observed in HCT116 cells following treatment with both UAs and their hybrids. Importantly, QDgreen/red themselves did not provoke toxic responses in cancer or normal cells. In conclusion, QDs are good candidates for targeted UA delivery carriers to cancer cells while protecting normal cells from toxic drug activities.

Pilch, J., et al. (2022). "Foliate-Targeting Quantum Dots-beta-Cyclodextrin Nanocarrier for Efficient Delivery of Unsymmetrical Bisacridines to Lung and Prostate Cancer Cells." Int J Mol Sci **23**(3).

Targeted drug delivery by nanocarriers molecules can increase the efficiency of cancer treatment. One of the targeting ligands is folic acid (FA), which has a high affinity for the folic acid receptors, which are overexpressed in many cancers. Herein, we describe the preparation of the nanoconjugates containing quantum dots (QDs) and beta-cyclodextrin (beta-CD) with foliate-targeting properties for the delivery of anticancer compound C-2028. C-2028 was

bound to the nanoconjugate via an inclusion complex with beta-CD. The effect of using FA in QDs-beta-CD(C-2028)-FA nanoconjugates on cytotoxicity, cellular uptake, and the mechanism of internalization in cancer (H460, Du-145, and LNCaP) and normal (MRC-5 and PNT1A) cells was investigated. The QDs-beta-CD(C-2028)-FA were characterized using DLS (dynamic light scattering), ZP (zeta potential), quartz crystal microbalance with dissipation (QCM-D), and UV-vis spectroscopy. The conjugation of C-2028 with non-toxic QDs or QDs-beta-CD-FA did not change the cytotoxicity of this compound. Confocal microscopy studies proved that the use of FA in nanoconjugates significantly increased the amount of delivered compound, especially to cancer cells. QDgreen-beta-CD(C-2028)-FA enters the cells through multiple endocytosis pathways in different levels, depending on the cell line. To conclude, the use of FA is a good self-navigating molecule in the QDs platform for drug delivery to cancer cells.

Pilch, J., et al. (2020). "New Unsymmetrical Bisacridine Derivatives Noncovalently Attached to Quaternary Quantum Dots Improve Cancer Therapy by Enhancing Cytotoxicity toward Cancer Cells and Protecting Normal Cells." ACS Appl Mater Interfaces **12**(15): 17276-17289.

The use of nanoparticles for the controlled drug delivery to cells has emerged as a good alternative to traditional systemic delivery. Quantum dots (QDs) offer potentially invaluable societal benefits such as drug targeting and in vivo biomedical imaging. In contrast, QDs may also pose risks to human health and the environment under certain conditions. Here, we demonstrated that a unique combination of nanocrystals core components (Ag-In-Zn-S) would eliminate the toxicity problem and increase their biomedical applications. The alloyed quaternary nanocrystals Ag-In-Zn-S (QDgreen, Ag1.0In1.2Zn5.6S9.4; QDred, Ag1.0In1.0Zn1.0S3.5) were used to transport new unsymmetrical bisacridine derivatives (UAs, C-2028 and C-2045) into lung H460 and colon HCT116 cancer cells for improving the cytotoxic and antitumor action of these compounds. UAs were coupled with QD through physical adsorption. The obtained results clearly indicate that the synthesized nanoconjugates exhibited higher cytotoxic activity than unbound compounds, especially toward lung H460 cancer cells. Importantly, unsymmetrical bisacridines noncovalently attached to QD strongly protect normal cells from the drug action. It is worth pointing out that QDgreen or QDred without UAs did not influence the growth of cancer and normal cells, which is consistent with in vivo results. In noncellular systems, at pH 5.5 and 4.0, which relates to the conditions of endosomes and lysosomes, the UAs were released from QD-UAs nanoconjugates. An increase of total lysosomes content was observed in H460 cells treated with QDs-UAs which can affect the release of the UAs from the conjugates. Moreover, confocal laser scanning microscopy analyses revealed that QD-UAs nanoconjugates enter H460 cells more efficiently than to HCT116 and normal cells, which may be the reason for their higher cytotoxicity against lung cancer. Summarizing, the noncovalent attachment of UAs to QDs increases the therapeutic efficiency of UAs by improving cytotoxicity toward lung H460 cancer cells and having protecting effects on normal cells.

Pilling, M. J., et al. (2017). "Quantum Cascade Laser Spectral Histopathology: Breast Cancer Diagnostics Using High Throughput Chemical Imaging." Anal Chem **89**(14): 7348-7355.

Fourier transform infrared (FT-IR) microscopy coupled with machine learning approaches has been demonstrated to be a powerful technique for identifying abnormalities in human tissue. The ability to objectively identify the prediseased state and diagnose cancer with high levels of accuracy has the potential to revolutionize current histopathological practice. Despite recent technological advances in FT-IR microscopy, sample throughput and speed of acquisition are key barriers to clinical translation. Wide-field quantum cascade laser (QCL) infrared imaging systems with large focal plane array detectors utilizing discrete frequency imaging have demonstrated that large tissue microarrays (TMA) can be imaged in a matter of minutes. However, this ground breaking technology is still in its infancy, and its applicability for routine disease diagnosis is, as yet, unproven. In light of this, we report on a large study utilizing a breast cancer TMA comprised of 207 different patients. We show that by using QCL imaging with continuous spectra acquired between 912 and 1800 cm(-1), we can accurately differentiate between 4 different histological classes. We demonstrate that we can discriminate between malignant and nonmalignant stroma spectra with high sensitivity (93.56%) and specificity (85.64%) for an independent test set. Finally, we classify each core in the TMA and achieve high diagnostic accuracy on a patient basis with 100% sensitivity and 86.67% specificity. The absence of false negatives reported here opens up the possibility of utilizing high throughput chemical imaging for cancer screening, thereby reducing pathologist workload and improving patient care.

Piloto, A. M. L., et al. (2022). "Cellulose-based hydrogel on quantum dots with molecularly imprinted polymers for the detection of CA19-9 protein cancer biomarker." Mikrochim Acta **189**(4): 134.

Molecularly imprinted polymers MIPs were successfully assembled around quantum dots (QDs), for the detection of the protein biomarker CA19-9

associated to pancreatic cancer (PC). These imprinted materials MIP@QDs were incorporated within the cellulose hydrogel with retention of its conformational structure inside the binding cavities. The concept is to use MIPs which function as the biorecognition elements, conjugated to cadmium telluride QDs as the sensing system. The excitation wavelength was set to 477 nm and the fluorescence signal was measured at its maximum intensity, with an emission range between 530 and 780 nm. The fluorescence quenching of the imprinted cellulose hydrogels occurred with increasing concentrations of CA19-9, showing linearity in the range 2.76 x 10 (-2) - 5.23 x 10 (2) U/ml, in a 1000-fold diluted human serum. Replicates of the imprinted hydrogel show a linear response below the cut-off values for pancreatic cancer diagnosis (< 23 U/ml), a limit of detection of 1.58 x 10 (-3) U/ml and an imprinting factor (IF) of 1.76. In addition to the fact that the imprinted cellulose hydrogel displays good stability and selectivity towards CA19-9 when compared with the non-imprinted controls, the conjugation of MIPs to QDs increases the sensitivity of the system for an optical detection method towards ranges within clinical significance. This fact shows potential for the imprinted hydrogel to be applied as a sensitive, low-cost format for point-of-care tests (PoCTs).

Porto, V., et al. (2018). "Silver Atomic Quantum Clusters of Three Atoms for Cancer Therapy: Targeting Chromatin Compaction to Increase the Therapeutic Index of Chemotherapy." Adv Mater: e1801317.

Nanomaterials with very low atomicity deserve consideration as potential pharmacological agents owing to their very small size and to their properties that can be precisely tuned with minor modifications to their size. Here, it is shown that silver clusters of three atoms (Ag3 -AQCs)-developed by an ad hoc method-augment chromatin accessibility. This effect only occurs during DNA replication. Coadministration of Ag3 -AQCs increases the cytotoxic effect of DNA-acting drugs on human lung carcinoma cells. In mice with orthotopic lung tumors, the coadministration of Ag3 -AQCs increases the amount of cisplatin (CDDP) bound to the tumor DNA by fivefold without modifying CDDP levels in normal tissues. As a result, CDDP coadministered with Ag3 -AQCs more strongly reduces the tumor burden. Evidence of the significance of targeting chromatin compaction to increase the therapeutic index of chemotherapy is now provided.

Pothipor, C., et al. (2021). "An electrochemical biosensor for simultaneous detection of breast cancer clinically related microRNAs based on a gold nanoparticles/graphene quantum dots/graphene oxide film." Analyst **146**(12): 4000-4009.

A label-free multiplexed electrochemical biosensor based on a gold nanoparticles/graphene quantum dots/graphene oxide (AuNPs/GQDs/GO) modified three-screen-printed carbon electrode (3SPCE) array is successfully constructed to detect miRNA-21, miRNA-155, and miRNA-210 biomarkers for the first time. Redox species (anthraquinone (AQ), methylene blue (MB), and polydopamine (PDA)) are used as redox indicators for anchoring capture miRNA probes, which hybridize with the complementary targets, miRNA-21, miRNA-155, and miRNA-210, respectively. After three target miRNAs are present, the square wave voltammetry (SWV) scan displays three well-separated peaks. Each peak indicates the presence of one miRNA, and its intensity quantitatively correlates with the concentration of the corresponding target analyte. This phenomenon results in the substantial decline of the SWV peak current of the redox probes. The developed AuNPs/GQDs/GO-based biosensor reveals excellent performance for simultaneous miRNA sensing. It offers a wide linear dynamic range from 0.001 to 1000 pM with ultrasensitive low detection limits of 0.04, 0.33, and 0.28 fM for the detection of miRNA-21, miRNA-155, and miRNA-210, respectively. It also presents high selectivity and applicability for the detection of miRNAs in human serum samples. This multiplex label-free miRNA biosensor has great potential for applications in breast cancer diagnosis.

Poulose, A. C., et al. (2012). "PEG coated biocompatible cadmium chalcogenide quantum dots for targeted imaging of cancer cells." J Fluoresc **22**(3): 931-944.

Cancer stands as a leading cause of mortality worldwide and diagnostics of cancer still faces drawbacks. Optical imaging of cancer would allow early diagnosis, evaluation of disease progression and therapy efficiency. To that aim, we have developed highly biocompatible PEG functionalized cadmium chalcogenide based three differently luminescent quantum dots (QDs) (CdS, CdSe and CdTe). Folate targeting scheme was utilized for targeting cancer cell line, MCF-7. We demonstrate the biocompatibility, specificity and efficiency of our nanotool in detection of cancer cells sparing normal cell lines with retained fluorescence of functionalized QDs as parental counterpart. This is the first time report of utilizing three differently fluorescent QDs and we have detailed about the internalization of these materials and time dependent saturation of targeting schemes. We present here the success of utilizing our biocompatible imaging tool for early diagnosis of cancer.

Przysiecka, L., et al. (2016). "iRGD peptide as effective transporter of CuInZnxS2+x quantum dots into human cancer cells." Colloids Surf B Biointerfaces **146**: 9-18.

In this paper, iRGD peptide-mediated quantum dots (QDs) delivery was studied. In the first step, dodecanethiol-capped CuInZnxS2+x (ZCIS) QDs were prepared and subsequently transferred into water using a standard and facile ligand exchange approach involving 3-mercaptopropionic acid (MPA). ZCIS@MPA nanocrystals possess a photoluminescence quantum yield (PL QY) of 25%, a PL emission centered at ca. 640nm and low distributions in size and shape. Next, the iRGD peptide was electrostatically associated to ZCIS@MPA QDs. After cytotoxicity evaluation, the tumor-targeting and penetrating activities of the iRGD/QD assembly were investigated by confocal microscopy. The experiments performed on various cancer cell lines revealed a high penetration ability of the assembly, while the bare QDs were not internalized. Additionally, imaging experiments were conducted on three-dimensional multicellular tumor spheroids in order to mimic the tumor microenvironment in vivo. iRGD/QD assemblies were found to be evenly distributed throughout the whole HeLa spheroid contrary to normal cells where they were not present. Therefore, iRGD/QD assemblies have a great potential to be used as targeted imaging agents and/or nanocarriers specific to cancer cells.

Qi, J., et al. (2021). "Heterobifunctional PEG-grafted black phosphorus quantum dots: "Three-in-One" nano-platforms for mitochondria-targeted photothermal cancer therapy." Asian J Pharm Sci **16**(2): 222-235.

Black phosphorus (BP) nano-materials, especially BP quantum dots (BPQDs), performs outstanding photothermal antitumor effects, excellent biocompatibility and biodegradability. However, there are several challenges to overcome before offering real benefits, such as poor stability, poor dispersibility as well as difficulty in tailoring other functions. Here, a "three-in-one" mitochondria-targeted BP nano-platform, called as BPQD-PEG-TPP, was designed. In this nano-platform, BPQDs were covalently grafted with a heterobifunctional PEG, in which one end was an aryl diazo group capable of reacting with BPQDs to form a covalent bond and the other end was a mitochondria-targeted triphenylphosphine (TPP) group. In addition to its excellent near-infrared photothermal properties, BPQD-PEG-TPP had much enhanced stability and dispersibility under physiological conditions, efficient mitochondria targeting and promoted ROS production through a photothermal effect. Both in vitro and in vivo experiments demonstrated that BPQD-PEG-TPP performed much superior photothermal cytotoxicity than BPQDs and BPQD-PEG as the mitochondria targeted PTT. Thus this "three-in-one" nanoplatform fabricated through polymer grafting, with excellent stability, dispersibility and negligible side effects, might be a promising strategy for mitochondria-targeted photothermal cancer therapy.

Qi, L., et al. (2021). "Biocompatible nucleus-targeted graphene quantum dots for selective killing of cancer cells via DNA damage." Commun Biol **4**(1): 214.

Graphene quantum dots (GQDs) are nano-sized graphene slices. With their small size, lamellar and aromatic-ring structure, GQDs tend to enter into the cell nucleus and interfere with DNA activity. Thus, GQD alone is expected to be an anticancer reagent. Herein, we developed GQDs that suppress the growth of tumor by selectively damaging the DNA of cancer cells. The amine-functionalized GQDs were modified with nucleus targeting TAT peptides (TAT-NGs) and further grafted with cancer-cell-targeting folic acid (FA) modified PEG via disulfide linkage (FAPEG-TNGs). The resulting FAPEG-TNGs exhibited good biocompatibility, nucleus uptake, and cancer cell targeting. They adsorb on DNA via the pi-pi and electrostatic interactions, which induce the DNA damage, the upregulation of the cell apoptosis related proteins, and the suppression of cancer cell growth, ultimately. This work presents a rational design of GQDs that induce the DNA damage to realize high therapeutic performance, leading to a distinct chemotherapy strategy for targeted tumor therapy.

Qian, J., et al. (2007). "Imaging pancreatic cancer using surface-functionalized quantum dots." J Phys Chem B **111**(25): 6969-6972.

In this study, CdSe/CdS/ZnS quantum dots (QDs) were used as optical contrast agent for imaging pancreatic cancer cells in vitro using transferrin and anti-Claudin-4 as targeting ligands. CdSe/CdS/ZnS was chosen because the CdSe/CdS/ZnS QDs have better photoluminescence (PL) efficiency and stability than those of CdSe/ZnS. The transferrin-mediated targeting is demonstrated in both a cell-free coprecipitation assay as well as using in vitro confocal microscopy. Pancreatic cancer specific uptake is also demonstrated using the monoclonal antibody anti-Claudin-4. This targeted QD platform will be further modified for the purpose of developing as an early detection imaging tool for pancreatic cancer.

Qin, M. Y., et al. (2015). "In vivo cancer targeting and fluorescence-CT dual-mode imaging with nanoprobes based on silver sulfide quantum dots and iodinated oil." Nanoscale **7**(46): 19484-19492.

In this article, a fluorescence-CT dual-mode nanoprobe is successfully synthesized by making use of distearoylphosphatidylethanolamine-poly(ethylene glycol)-folate (DSPE-PEG2000-FA) and other amphiphilic molecules to coat silver sulfide (Ag2S) quantum dots (QDs) and iodinated oil simultaneously.

In vitro experiments show that the fluorescence wavelength of the nanoprobe is 1170 nm in the near infrared-II region. Its size is 139.6 nm, it has good dispersibility, and it has low cellular toxicity at concentrations up to 25 mug mL(-1) Ag. In vivo experiments revealed that the probe has a rather long circulation time (blood half-life of 5.7 hours), and the tissue histopathological tests show that it is not obviously harmful to major organs' normal function. Biochemical analysis (glutamic pyruvic transaminase and glutamic oxaloacetic transaminase levels) and blood analysis (white blood cell, red blood cell, hemoglobin and blood platelet counts) reveal that it has little influence on blood within 15 days of administration. When injected into HeLa xenograft nude mice by the tail vein, the probe elicited intensely enhanced fluorescence and X-ray computed tomography (CT) signals in the tumors after 24 hours, and the structure, size and position of tumor tissue were shown clearly. In a word, the probe has good tumor targeting capabilities, and it has significant value in fluorescence-CT dual-mode imaging in vivo.

Qiu, Y., et al. (2017). "Novel Single-Cell Analysis Platform Based on a Solid-State Zinc-Coadsorbed Carbon Quantum Dots Electrochemiluminescence Probe for the Evaluation of CD44 Expression on Breast Cancer Cells." ACS Appl Mater Interfaces **9**(20): 16848-16856.

A novel single-cell analysis platform was fabricated using solid-state zinc-coadsorbed carbon quantum dot (ZnCQDs) nanocomposites as an electrochemiluminescence (ECL) probe for the detection of breast cancer cells and evaluation of the CD44 expression level. Solid-state ZnCQDs nanocomposite probes were constructed through the attachment of ZnCQDs to gold nanoparticles and then the loading of magnetic beads to amplify the ECL signal, exhibiting a remarkable 120-fold enhancement of the ECL intensity. Hyaluronic acid (HA)-functionalized solid-state probes were used to label a single breast cancer cell by the specific recognition of HA with CD44 on the cell surface, revealing more stable, sensitive, and effective tagging in comparison with the water-soluble CQDs. This strategy exhibited a good analytical performance for the analysis of MDA-MB-231 and MCF-7 single cells with linear range from 1 to 18 and from 1 to 12 cells, respectively. Furthermore, this single-cell analysis platform was used for evaluation of the CD44 expression level of these two cell lines, in which the MDA-MB-231 cells revealed a 2.8-5.2-fold higher CD44 expression level. A total of 20 single cells were analyzed individually, and the distributions of the ECL intensity revealed larger variations, indicating the high cellular heterogeneity of the CD44 expression level on the same cell line. The as-proposed single-cell analysis platform might provide a novel protocol to effectively study the individual cellular function and cellular heterogeneity.

Radenkovic, D., et al. (2016). "Quantum dot nanoparticle for optimization of breast cancer diagnostics and therapy in a clinical setting." Nanomedicine **12**(6): 1581-1592.

Breast cancer is the most common cancer in the world. Sentinel lymph node (SLN) biopsy is used for staging of axillary lymph nodes. Organic dyes and radiocolloid are currently used for SLN mapping, but expose patients to ionizing radiation, are unstable during surgery and cause local tissue damage. Quantum dots (QD) could be used for SLN mapping without the need for biopsy. Surgical resection of the primary tumor is the optimal treatment for early-diagnosed breast cancer, but due to difficulties in defining tumor margins, cancer cells often remain leading to reoccurrences. Functionalized QD could be used for image-guided tumor resection to allow visualization of cancer cells. Near Infrared QD are photostable and have improved deep tissue penetration. Slow elimination of QD raises concerns of potential accumulation. Nevertheless, promising findings with cadmium-free QD in recent in vivo studies and first in-human trial suggest huge potential for cancer diagnostic and therapy.

Rahman, M. M., et al. (2021). "Cytotoxicity Study of Cadmium-Selenium Quantum Dots (Cdse QDs) for Destroying the Human HepG2 Liver Cancer Cell." J Biomed Nanotechnol **17**(11): 2153-2164.

In this approach, Hepatocellular carcinoma (HCC) is originated from hepatocytes cell, which can spread several parts in the body. It increases the death rate of cancer patients and more common in men rather than female. Patients having large tumor are growing through expensive treatment such as chemotherapy, radiotherapy and surgery. Nano medicine such as nano-dimensional particles as well as quantum dots might be an alternative treatment with greater efficiency in cancer biology field. Modification of surface and chemical properties of cadmium groups quantum dots can easily penetrate into the cancer cell without harming normal tissues. Here, Cadmium-Selenium Quantum Dot nanomaterials (CdSe QDs) have been prepared in solution phase with 0.1 M concentration, which was potentially applied for the destroying of HepG2 cancer cell with 24 hour and 36 hour of incubation. Due to their size, surface properties, lower cost, QDs can easily attached to the cell and able to damage the cells more rapidly in vitro process. For cell death, gene expression and morphological changing analysis were completed MTT, Flow Cytometry, qRT-PCR assay. Finally, the cell deaths were observed by cell shrinkage, rupture of membrane and expression of apoptotic gene (Bcl2, Beta

catenin, Bax) were positive comparing untreated HepG2 cell line.

Rajender, G., et al. (2019). "Solvent dependent synthesis of edge-controlled graphene quantum dots with high photoluminescence quantum yield and their application in confocal imaging of cancer cells." J Colloid Interface Sci **541**: 387-398.

We report on the synthesis of edge-controlled and highly fluorescent few-layer graphene quantum dots (GQDs) using different solvents and explore their application in the confocal imaging of cancer cells. TEM and AFM imaging analysis reveal that GQDs of sizes in the range 5-8nm and few-layer (1-4) thickness were grown using DMF, DMSO, and water as solvents. Micro-Raman analysis reveals that GQDs grown with DMF possess primarily the armchair edges, while that grown with water contains primarily the zigzag edges. The nature of oxygen functional groups on the edge/in-plane sites of carbon atoms was elucidated through thermogravimetric and FTIR analyses. The GQDs containing high density of armchair edges and oxygen functional group defects exhibited high photoluminescence (PL) quantum yield (approximately 32%). The time-resolved PL measurements suggest the charge transfer from the GQDs to the surrounding dielectric medium. Further, we explore the high PL quantum yield of GQDs in bio-imaging of A-375 and HeLa cancer cells. The cell viability of GQDs on A-375 cells was found to be considerably higher than that of HeLa cells at a GQD concentration of 44.4microg/mL, which is very significant. Our results indicate the GQD edge site dependent cell viability, for the first time. These results will be useful for the development of highly fluorescent GQDs with specific edge structure and their exploration in the field of bio-imaging, bio-sensing, and drug delivery applications.

Rakovich, A. and T. Rakovich (2018). "Semiconductor versus graphene quantum dots as fluorescent probes for cancer diagnosis and therapy applications." J Mater Chem B **6**(18): 2690-2712.

Early diagnosis of cancer is of critical importance in determining the outcome of a patient, and nanoparticulate fluorophores have been at the centre of research for such applications owing to their superior optical properties. Furthermore, the large surface area to volume ratios of these fluorophores enables them to be endowed with several modalities, including the targeting of specific biomarkers and drug delivery capabilities, promoting them as therapeutic agents as well. Over the last few decades, semiconductor quantum dots have dominated the field due to their unique yet well characterised optical properties. However, the scope of their application for diagnosis and therapy of cancer has been hindered by declarations of in vivo toxicity attributed to heavy metals typically found in their composition. Recent arrivals graphene quantum dots, or carbon-derived counterparts to SQDs, are often claimed to be biocompatible but they have complicated optical properties. In this review, we compare the properties of these two types of quantum dots in view of their employment as fluorescent agents for cancer diagnosis and therapy.

Rakovich, T. Y., et al. (2014). "Highly sensitive single domain antibody-quantum dot conjugates for detection of HER2 biomarker in lung and breast cancer cells." ACS Nano **8**(6): 5682-5695.

Despite the widespread availability of immunohistochemical and other methodologies for screening and early detection of lung and breast cancer biomarkers, diagnosis of the early stage of cancers can be difficult and prone to error. The identification and validation of early biomarkers specific to lung and breast cancers, which would permit the development of more sensitive methods for detection of early disease onset, is urgently needed. In this paper, ultra-small and bright nanoprobes based on quantum dots (QDs) conjugated to single domain anti-HER2 (human epidermal growth factor receptor 2) antibodies (sdAbs) were applied for immunolabeling of breast and lung cancer cell lines, and their performance was compared to that of anti-HER2 monoclonal antibodies conjugated to conventional organic dyes Alexa Fluor 488 and Alexa Fluor 568. The sdAbs-QD conjugates achieved superior staining in a panel of lung cancer cell lines with differential HER2 expression. This shows their outstanding potential for the development of more sensitive assays for early detection of cancer biomarkers.

Ranjbar-Navazi, Z., et al. (2018). "Doxorubicin-conjugated D-glucosamine- and folate- bi-functionalised InP/ZnS quantum dots for cancer cells imaging and therapy." J Drug Target **26**(3): 267-277.

Nanoscaled quantum dots (QDs), with unique optical properties have been used for the development of theranostics. Here, InP/ZnS QDs were synthesised and functionalised with folate (QD-FA), D-glucosamine (QD-GA) or both (QD-FA-GA). The bi-functionalised QDs were further conjugated with doxorubicin (QD-FA-GA-DOX). Optimum Indium to fatty acid (In:MA) ratio was 1:3.5. Transmission electron microscopy (TEM) micrographs revealed spherical morphology for the QDs (11 nm). Energy-dispersive spectroscopy (EDS) spectrum confirmed the chemical composition of the QDs. MTT analysis in the OVCAR-3 cells treated with bare QDs, QD-FA, QD-GA, QD-FA-GA and QD-FA-GA-DOX (0.2 mg/mL of QDs) after 24 h indicated low toxicity for the bare QDs and functionalised QDs (about 80-90% cell viability). QD-FA-GA-DOX nanoparticles elicited toxicity in the cells. Cellular

uptake of the engineered QDs were investigated in both folate receptor (FR)-positive OVCAR-3 cells and FR-negative A549 cells using fluorescence microscopy and FACS flow cytometry. The FA-functionalised QDs showed significantly higher uptake in the FR-positive OVCAR-3 cells, nonetheless the GA-functionalised QDs resulted in an indiscriminate uptake in both cell lines. In conclusion, our findings indicated that DOX-conjugated FA-armed QDs can be used as theranostics for simultaneous imaging and therapy of cancer.

Rehman, Y., et al. (2021). "Theranostic two-dimensional superparamagnetic maghemite quantum structures for ROS-mediated cancer therapy." J Mater Chem B **9**(29): 5805-5817.

In this work, size- and shape-controlled two-dimensional (2D) superparamagnetic maghemite (gamma-Fe2O3) quantum flakes (MQFs) with high surface area and mesoporosity were prepared by facile hydrothermal synthesis for biological applications. These quantum flakes exhibited superparamagnetic behaviours over a wide temperature range of 75-950 K with high saturation magnetization of Ms - 23 emu g-1 and a lower coercivity of Hc - 6.1 Oe. MQFs also demonstrated a good colloidal stability and a positively charged flake surface. Selective toxicity dependent upon selective ROS scavenging/generation and cellular MQF uptake towards non-malignant human keratinocyte (HaCaT) and malignant melanoma (A357) and human breast cancer (MDA-MB 231) cell lines were witnessed. An increased ROS concentration resulted due to the peroxidase-like activity of MQFs in malignant cells. In contrast, ROS scavenging was observed in non-malignant cells due to dominant catalase-like activity. In vitro fluorescence properties added the diagnostic ability to the ambit of MQFs. Furthermore, the therapeutic efficiency could be significantly enhanced by the hyperthermic (25-47 degrees C) ability of MQF in cancerous cells. Our findings reveal the novel theranostic MQF structure with immense cancer therapeutic potential via augmentation of ROS generation by hyperthermia in a selective microenvironment.

Riquet, M., et al. (2010). "Lung cancer invading the pericardium: quantum of lymph nodes." Ann Thorac Surg **90**(6): 1773-1777.

BACKGROUND: Lung cancer may invade the pericardium (T3) and the intrapericardial pulmonary veins and left atrium (T4). Our purpose was to analyze the characteristics of this invading process in search of the reasons explaining its poor prognosis. METHODS: The clinical records of 4,668 patients who underwent surgery for lung cancer between January 1983 and December 2006 in two thoracic surgery centers were retrospectively reviewed. The epidemiology, pathology, and prognostic characteristics of the tumors invading the pericardium alone (T3) or with pulmonary veins and atrium (T4) were analyzed and compared with all other tumors. RESULTS: There were 75 male and 16 female patients, with 85 pneumonectomies and 6 lobectomies that proved R0 in 59.3% of patients, and contained 69 squamous cell cancers, 11 adenocarcinomas, and 13 miscellaneous tumors; 12 were N0 (13.2%), 31 were N1 (34.1%), and 48 were N2 (52.8%). Pericardium alone was invaded in 32 patients (35.2%), and with pulmonary vein and atrium in 34 (37.3%) and 25 (27.5%), respectively. Patient characteristics were similar in each group. Five-year and 10-year survival rates were 15.1% and 10.4%, respectively. Frequency of pneumonectomy, R1-2 resection, and N1-2 involvement were significantly more important compared with noninvading tumors ($p < 10(-6)$). CONCLUSIONS: Reports on T3 and T4 cancer with pericardial involvement are few, but also stress that pulmonary vein and left atrium invasion does not worsen the prognosis more than pericardial invasion alone. The rich pericardial lymph drainage might enhance the spread of tumor cells, explaining excessively high N1-N2 rates and pericardial invasion-related poor prognosis.

Roshini, A., et al. (2018). "pH-sensitive tangeretin-ZnO quantum dots exert apoptotic and anti-metastatic effects in metastatic lung cancer cell line." Mater Sci Eng C Mater Biol Appl **92**: 477-488.

Most cancer patients die as a consequence of distant metastases, which are frequently unresponsive to cancer therapy. This study focuses on the anti-tumorigenic and anti-metastatic properties of tangeretin-zinc oxide quantum dots (Tan-ZnO QDs) against the NCI-H358 cell line. Tan-ZnO QDs are pH-sensitive and capitalize on the acidic pH maintained in the tumor microenvironment; therefore, targeted drug delivery is directed specifically to cancer cells, leaving the normal cells less affected. Tan was loaded into synthesized ZnO QDs, and drug loading was analyzed using Fourier transform infrared (FTIR) spectroscopy and ultraviolet-visible (UV-Vis) spectrometry. Crystalline phase and particle size were measured using transmission electron microscopy (TEM) and X-ray diffraction (XRD). Drug release was evaluated in buffered solutions with differing pH for up to 15h. The results confirmed stable drug release (80%) in an acidic pH. Tan-ZnO QDs induced significant cytotoxicity in NCI-H358 metastatic cells, while not markedly affecting HK-2 human normal cells. Morphology of treated H358 cells analyzed via atomic force microscopy (AFM) showed an increased surface roughness and pores. Further, the number of terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive cells increased after treatment with Tan-ZnO QDs. DNA fragmentation was also induced after treatment with increasing

concentrations of Tan-ZnO QDs in H358 cells. We also confirmed regulation of apoptosis via expression levels of Bax and Bcl-2 proteins; G2/M phase cell cycle arrest was observed. Additionally, cell proliferation and migration drastically decreased, and cell invasion and migration, hallmarks of metastasis, were significantly inhibited in H358 cells. Matrix metalloproteinase (MMP)2 and MMP9, markers of metastasis, as well as vascular endothelial growth factor (VEGF), a marker of angiogenesis, were significantly downregulated upon treatment with Tan-ZnO QDs. In conclusion, our novel formulation destabilized H358 cells by using its acidic tumor microenvironment, thereby regulating cell apoptosis, proliferation, and metastatic properties.

Ross, W. S. (1972). "Cancer: the quantum leap." Dent Stud **50**(8): 74-77.

Roy, S., et al. (2021). "Targeted Bioimaging of Cancer Cells Using Free Folic Acid-Sensitive Molybdenum Disulfide Quantum Dots through Fluorescence "Turn-Off"." ACS Appl Bio Mater **4**(3): 2839-2849.

In the present study, a proficient way for targeted bioimaging of folate receptor (FR)-positive cancer cells using free folic acid (FA)- and MoS2 QD-based nanoprobes is discussed along with its advantages over the preparation of orthodox direct FA-nanoprobe bioconjugates for the imaging. The water-soluble MoS2 QDs of size 4-5 nm with cysteine functionalization are synthesized by a simplistic bottom-up hydrothermal method. The as-prepared MoS2 QDs exhibit the blue emission with the highest emission intensity at 444 nm upon excitation of 370 nm. The MoS2 QDs are too sensitive toward FA to produce an effective and stable nanofiber structure through supramolecular interaction, which demonstrates approximately 97% quenching of fluorescence. Moreover, the high selectivity and sensitivity of MoS2 QDs toward FA make the MoS2 QD-based nanoprobe an appropriate candidate for FA-targeted "turn-off" imaging probes for in vivo study of FA-pretreated FR-overexpressed cancer cells. It is obvious from the confocal microscopy images that the FA-pretreated B16F10 cancer cells show higher population of dimmed fluorescence compared to untreated cancer cells and HEK-293 normal cells. The flow cytometry study quantitatively reveals the significant difference of the geometric mean of fluorescence between FA-pretreated and untreated B16F10 cancer cells. Hence, these MoS2 QD-based nanoprobes can be applied as potential nanoprobes for the prediagnosis of cancer through targeted bioimaging.

Ruan, J., et al. (2012). "HER2 monoclonal antibody conjugated RNase-A-associated CdTe quantum dots for targeted imaging and therapy of gastric cancer." Biomaterials **33**(29): 7093-7102.

Successful development of safe and effective nanoprobes for targeted imaging and selective therapy of in-situ gastric cancer is a great challenge. Herein, one kind of multifunctional HER2 monoclonal antibody conjugated RNase A-associated CdTe quantum dot cluster (HER2-RQDs) nanoprobes was prepared, its cytotoxicity was evaluated. Subcutaneous gastric cancer nude mouse models and in-situ gastric cancer SCID mouse models were established, and were intravenously injected HER2-RQDs nanoprobes, the bio-distribution and therapeutic effects of HER2-RQDs in vivo were evaluated. Results showed that HER2-RQDs nanoprobes could selectively kill gastric cancer MGC803 cells, could target imaging subcutaneous gastric cancer cells at 3 h post-injection, and in-situ gastric cancer cells at 6 h post-injection, and could inhibit the growth of gastric cancer tissues and extended survival time of gastric cancer bearing mouse models, which is closely associated with destroying functional RNAs in cytoplasm by RNase A released from HER2-RQDs nanoprobes, preventing protein synthesis and inducing cell apoptosis. High-performance HER2-RQDs nanoprobes exhibit great potential in applications such as in-situ gastric cancer targeted imaging, and selective therapy in the near future.

Ruan, Y., et al. (2012). "Detection of prostate stem cell antigen expression in human prostate cancer using quantum-dot-based technology." Sensors (Basel) **12**(5): 5461-5470.

Quantum dots (QDs) are a new class of fluorescent labeling for biological and biomedical applications. In this study, we detected prostate stem cell antigen (PSCA) expression correlated with tumor grade and stage in human prostate cancer by QDs-based immunolabeling and conventional immunohistochemistry (IHC), and evaluated the sensitivity and stability of QDs-based immunolabeling in comparison with IHC. Our data revealed that increasing levels of PSCA expression accompanied advanced tumor grade (QDs labeling, $r = 0.732$, $p < 0.001$; IHC, $r = 0.683$, $p < 0.001$) and stage (QDs labeling, $r = 0.514$, $p = 0.001$; IHC, $r = 0.432$, $p = 0.005$), and the similar tendency was detected by the two methods. In addition, by comparison between the two methods, QDs labeling was consistent with IHC in detecting the expression of PSCA in human prostate tissue correlated with different pathological types ($K = 0.845$, $p < 0.001$). During the observation time, QDs exhibited superior stability. The intensity of QDs fluorescence remained stable for two weeks ($p = 0.083$) after conjugation to the PSCA protein, and nearly 93% of positive expression with their fluorescence still could be seen after four weeks.

Ruan, Y., et al. (2011). "Comparison of quantum-dots- and fluorescein-isothiocyanate-based technology for detecting prostate-specific antigen expression in human prostate cancer." IET Nanobiotechnol **5**(2): 47.

Quantum dots (QDs) are a new class of fluorescent labelling for biological and biomedical applications. In this study, the authors evaluated the sensitivity and stability of quantum-dots-based immunolabelling, in comparison with the conventional fluorescein-isothiocyanate-based immunolabelling (FITC), for detecting prostate-specific antigen (PSA) expression in human prostate cancer. The authors' data revealed that the two methods had similar sensitivity in differential display of the PSA expression correlated with tumour stage and grade (=0.88, p<0.001). Moreover, the intensity of QDs fluorescence remain stable for 10 days after conjugation to the PSA protein in 97% of the cases and more than 1 month in 92% of the cases, although the FITC fluorescence became undetectable after 6 min for all cases.

SalmanOgli, A. (2011). "Nanobio applications of quantum dots in cancer: imaging, sensing, and targeting." Cancer Nanotechnol **2**(1-6): 1-19.

In this article, the syntheses and optical properties of core/shell quantum dot (CdSe/ZnS) and their applications are reviewed. Nevertheless, the main focus is to provide an overview on biological applications of quantum dots that contain imaging, targeting, and sensing. We discuss the different synthetic methods, optical properties (photoluminescence intensity, absorption, and fluorescence spectra), and their dependence on shape, size, and inner structure of quantum dots. Also, the different mechanisms of quantum dots bio-targeting (passive and active mechanisms) are discussed. The impact of quantum dots in bioimaging is reviewed regarding its photoluminescence intensity, absorption and emission spectrum, and photo-stability on high-quality and sensitivity imaging. Further, the difference between near infrared and visible emission quantum dots in deep tissue imaging will be reviewed and some of done works are considered and compared with each other. And finally, the biosensing potential/application of quantum dots in medical diagnosis is going to be highlighted.

Santana-Blank, L., et al. (2016). ""Quantum Leap" in Photobiomodulation Therapy Ushers in a New Generation of Light-Based Treatments for Cancer and Other Complex Diseases: Perspective and Mini-Review." Photomed Laser Surg **34**(3): 93-101.

OBJECTIVE: Set within the context of the 2015 International Year of Light and Light-Based Technologies,and of a growing and aging world population with ever-rising healthcare needs, this perspective and mini-review focuses on photobiomodulation (PBM) therapy as an emerging, cost-effective, treatment option for cancer (i.e., solid tumors) and other complex diseases, particularly, of the eye (e.g., age-related macular degeneration, diabetic retinopathy, glaucoma, retinitis pigmentosa) and the central nervous system (e.g., Alzheimer's and Parkinson's disease). BACKGROUND DATA: Over the last decades, primary and secondary mechanisms of PBM have been revealed. These include oxygen-dependent and oxygen-independent structural and functional action pathways. Signal and target characteristics determine biological outcome, which is optimal (or even positive) only within a given set of parameters. METHODS: This study was a perspective and nonsystematic literature mini-review. RESULTS: Studies support what we describe as a paradigm shift or "quantum leap" in the understanding and use of light and its interaction with water and other relevant photo-cceptors to restore physiologic function. CONCLUSIONS: Based on existing evidence, it is argued that PBM therapy can raise the standard of care and improve the quality of life of patients for a fraction of the cost of many current approaches. PBM therapy can, therefore,benefit large, vulnerable population groups, including the elderly and the poor, whilehaving a major impact on medical practice and public finances.

Sappati, S., et al. (2016). "Nuclear quantum effects in a HIV/cancer inhibitor: The case of ellipticine." J Chem Phys **145**(20): 205102.

Ellipticine is a natural product that is currently being actively investigated for its inhibitory cancer and HIV properties. Here we use path-integral molecular dynamics coupled with excited state calculations to characterize the role of nuclear quantum effects on the structural and electronic properties of ellipticine in water, a common biological solvent. Quantum effects collectively enhance the fluctuations of both light and heavy nuclei of the covalent and hydrogen bonds in ellipticine. In particular, for the ellipticine-water system, where the proton donor and acceptor have different proton affinities, we find that nuclear quantum effects (NQEs) strengthen both the strong and the weak H bonds. This is in contrast to what is observed for the cases where the proton affinity of the donors and acceptors is same. These structural fluctuations cause a significant red-shift in the absorption spectra and an increase in the broadening, bringing it into closer agreement with the experiments. Our work shows that nuclear quantum effects alter both qualitatively and quantitatively the optical properties of this biologically relevant system and highlights the importance of the inclusion of these effects in the microscopic understanding of their optical properties. We propose

that isotopic substitution will produce a blue shift and a reduction in the broadening of the absorption peak.

Savla, R., et al. (2011). "Tumor targeted quantum dot-mucin 1 aptamer-doxorubicin conjugate for imaging and treatment of cancer." J Control Release **153**(1): 16-22.

In this study, we report the design and delivery of a tumor-targeted, pH-responsive quantum dot-mucin1 aptamer-doxorubicin (QD-MUC1-DOX) conjugate for the chemotherapy of ovarian cancer. To achieve active cancer targeting, QD was conjugated with a DNA aptamer specific for mutated MUC1 mucin overexpressed in many cancer cells including ovarian carcinoma. DOX was attached to QD via a pH-sensitive hydrazone bond in order to provide the stability of the complex in systemic circulation and drug release in acidic environment inside cancer cells. The data show that this bond is stable at neutral and slightly basic pH and undergoes rapid hydrolysis in mildly acidic pH. Confocal microscopy and in vivo imaging studies show that the developed QD-MUC1-DOX conjugate had higher cytotoxicity than free DOX in multidrug resistant cancer cells and preferentially accumulated in ovarian tumor. Data obtained demonstrate a high potential of the proposed conjugate in treatment of multidrug resistant ovarian cancer.

Shafi, A., et al. (2020). "Molecular docking, quantum chemical computational and vibrational studies on bicyclic heterocycle "6-nitro-2,3-dihydro-1,4-benzodioxine": Anti-cancer agent." Comput Biol Chem **86**: 107226.

The heterocyclic aromatic compounds are primarily used to make pharmaceutical and agrochemicals. In addition, these compounds can be chosen as antioxidants, corrosion inhibitors, electro and opto-electronic devices, polymer material, dye stuff, developers, etc. On the account of this, the heterocyclic aromatic 6-nitro-2,3-dihydro-1,4-benzodioxine (6N3DB) was chosen and the structure is optimized to predict the important properties of it. The structural parameters such as bond length and bond angle have been obtained by DFT/B3LYP/6-311++G(d,p) basis set to know the geometry and orientation of 6N3DB. The molecule has been characterized by FT-IR and FT-Raman spectroscopic techniques to predict the functional groups, vibrational modes and aromatic nature of 6N3DB. The chemical shifts of (1)H and (13)C have been obtained experimentally and compared with the theoretical data. The parameters such as the band gap between HOMO-LUMO orbitals, lambdamax, and electron transition probability in frontier orbitals have been estimated to know the NLO and corrosion inhibition activity. HOMO-LUMO orbital diagram has been obtained for different energy levels and their band gap energies have been compared with UV-vis band gap values. The chemical significance of the molecule has been explained using ELF, LOL, and RDG. The binding energy and intermolecular energy values indicate that the title compound possesses anti-cancer property through hydrolase inhibition activity.

Shao, D., et al. (2014). "Selective inhibition of liver cancer growth realized by the intrinsic toxicity of a quantum dot-lipid complex." Int J Nanomedicine **9**: 5753-5769.

Using the intrinsic toxicity of nanomaterials for anticancer therapy is an emerging concept. In this work, we discovered that CdTe/CdS quantum dots, when coated with lipids (QD-LC) instead of popular liposomes, polymers, or dendrimers, demonstrated extraordinarily high specificity for cancer cells, which was due to the difference in the macropinocytosis uptake pathways of QD-LC between the cancer cells and the normal cells. QD-LC-induced HepG2 cell apoptosis was concomitant with the activation of the JNK/caspase-3 signaling pathway. Moreover, QD-LC treatment resulted in a delay in the latent period for microtumor formation of mouse hepatocarcinoma H22 cells and inhibited tumor growth, with a reduction of 53.2% in tumor volume without toxicity in major organs after intratumoral administrations to tumor-bearing mice. Our results demonstrate that QD-LC could be a very promising theranostic agent against liver cancer.

Shao, D., et al. (2015). "Noninvasive theranostic imaging of HSV-TK/GCV suicide gene therapy in liver cancer by folate-targeted quantum dot-based liposomes." Biomater Sci **3**(6): 833-841.

Theranostics is emerging as a popular strategy for cancer therapy; thanks to the development of nanotechnology. In this work, we have combined an HSV-TK/GCV suicide gene system and near-infrared quantum dots, as the former is quite effective in liver cancer treatment and the latter facilitates tumor imaging. A folate-modified theranostic liposome (FL/QD-TK) was developed, which is composed of an HSV-TK suicide gene covalently coupling with near-infrared fluorescent CdSeTe/ZnS core/shell quantum dots. The liver cancer-targeting and biosafety of FL/QD-TK were studied in vitro and in vivo. FL/QD-TK exhibited highly specific tumor imaging and strong inhibition of the folate receptor-overexpressed Bel-7402 mouse xenografts without systematic toxicity. This study may shed light on gene delivery and targeted cancer therapy.

Shao, D., et al. (2012). "Monitoring HSV-TK/ganciclovir cancer suicide gene therapy using CdTe/CdS core/shell quantum dots." Biomaterials **33**(17): 4336-4344.

To be able to label a gene and monitor its migration are key important approaches for the clinical

application of cancer suicide gene therapy. Photonic nanomaterials are introduced in this work. One of the most promised suicide genes - herpes simplex virus thymidine kinase (HSV-TK) gene - is successfully linked with CdTe/CdS core/shell quantum dots (QDs) via EDC/NHS coupling method. From confocal microscopy it was demonstrated that plasmid TK intracellular trafficking can be effectively and distinctly traced via monitoring the luminescence of the QDs up to 96 h after transfection of QDs-TK conjugates into Hela cells. MTT results show that the QDs-TK conjugates have a high efficient cytotoxicity after adding GCV into Hela cells, whereas the QDs exert no detectable deleterious effects on the cellular processes. The apoptosis induced by QDs-TK conjugates with GCV is distinctly traced partly due to the strong luminescence of the QDs. Our results indicate that photonic nanomaterials, e.g. QDs, provide a tool for monitoring TK gene delivery and anti-cancer activity.

Sharma, A., et al. (2013). "Quantum dots self assembly based interface for blood cancer detection." Langmuir **29**(27): 8753-8762.

Results of the studies related to fabrication of sensitive electrochemical biosensor using an interface based on quantum dots (QDs) self-assembly is reported. The QDs assembly is sought to provide improved fundamental characteristics to the electrode interface in terms of electroactive surface area, diffusion coefficient, and electron transfer kinetics. This QDs modified electrode has been utilized to serve as a transducer surface for covalent immobilization of chronic myelogenous leukemia (CML) specific probe oligonucleotide, designed from the BCR-ABL fusion gene. The electrochemical characteristics of this biosensor toward various designed synthetic oligonucleotides reveal a significant enhancement in its mismatch discrimination capability compared to the biosensing assay without QDs under similar experimental conditions. The sensing characteristics of this biosensor offer a potential for detection of target oligonucleotide at a concentration as low as 1.0 pM. Furthermore, the PCR-amplified CML-positive patient samples with various BCR-ABL transcript ratios can be electrochemically distinguished from healthy samples, indicating promising application of the QDs based biosensor for clinical investigations.

Shi, C., et al. (2019). "N,S-self-doped carbon quantum dots from fungus fibers for sensing tetracyclines and for bioimaging cancer cells." Mater Sci Eng C Mater Biol Appl **105**: 110132.

In this work, nitrogen and sulfur dual-doped carbon quantum dots (N,S-CDs) from naturally renewable biomaterial fungus fibers were prepared by a biosynthesis and hydrothermal method. The N,S-CDs displayed good water solubility, excellent stability, high quantum yield (QY=28.11%) as well as remarkable features for fluorescence quenching-based detection and cellular imaging of cancer cells. It was worth mentioning that the heteroatoms doped carbon quantum dots made from the fungus fibers had a satisfactory QY and could be used as a selective, efficient, and sensitive fluorescent probe to determine tetracyclines by the synergistic effects of static quenching and internal filtration effect. The probe demonstrated a wide linear range and low detection limit. For tetracycline, the linear range was 0.5muM to 47.6muM, and the corresponding detection limit was 15.6nM. Significantly, the test papers prepared by using N,S-CDs could detect tetracyclines in aquiculture wastewater rapidly. The produced N,S-CDs did not affect the cell viability and showed great promises for cellular imaging.

Shi, C., et al. (2008). "Quantum dots-based multiplexed immunohistochemistry of protein expression in human prostate cancer cells." Eur J Histochem **52**(2): 127-134.

Semiconductor quantum dots (QDs) are bright fluorescent nanoparticles that have been successfully used for the detection of biomarker expression in cells. The objective of the present study is to use this technology in a multiplexing manner to determine at a single cell level the expression of a cell-specific bio-marker, prostate-specific antigen (PSA) expressed by human prostate cancer LNCaP and ARCaP cell lines. Here we compared the sensitivity of immunohistochemistry (IHC) and QD-based detection of AR and PSA expression in these cell lines. Further, we conducted multiplexing QD-based detection of PSA and androgen receptor (AR) expression in LNCaP cells subjecting to androgen (R1881) stimulation. The involvement of AR in PSA regulation in LNCaP cells, at a single cell level, was confirmed by the co-incubation of LNCaP cells in the presence of both R1881 and its receptor antagonist, bicalutamide (Casodex). We showed here the superior quality of QDs, in comparison to IHC, for the detection of AR and PSA in cultured LNCaP and ARCaP cells. Multiplexing QDs technique can be used to detect simultaneously AR and PSA expression induced by R1881 which promoted AR translocation from its cytosolic to the nuclear compartment. We observed AR antagonist, bicalutamide, inhibited AR nuclear translocation and PSA, but not AR expression in LNCaP cells.

Shi, C., et al. (2009). "Visualizing human prostate cancer cells in mouse skeleton using bioconjugated near-infrared fluorescent quantum dots." Urology **74**(2): 446-451.

OBJECTIVES: To visualize human prostate cancer cells in mouse bone with bioconjugated near-infrared quantum dot (QD) probes. Near-infrared

fluorescent probes using QDs can visualize tumors in deep tissues in vivo. METHODS: Human prostate cancer C4-2B xenografts grown in mouse tibia were detected by prostate-specific membrane antigen antibody conjugated with QDs emitting light at the near-infrared range of 800 nm (QD800). Images in culture and in vivo were acquired using the IVIS Imaging System. RESULTS: As few as 5000 cells can be detected subcutaneously when tagged with QD800 conjugate and injected directly into mice. QD800 conjugate injected intravenously in mice harboring C4-2B tumors in tibia detected signals from a minimum of 500 000 cells. The maximal light emission was detected 30 minutes after intravenous injection of QD800 conjugate in mice with established C4-2B tumors. CONCLUSIONS: Bioconjugated near-infrared QD probes are highly sensitive molecular imaging tools for human prostate cancer micrometastases in mice.

Shi, X., et al. (2020). "Targeted Fluorescence Imaging and Biological Effects of Peptide Conjugated Quantum Dots on Pancreatic Cancer Cells." J Nanosci Nanotechnol **20**(3): 1351-1357.

Arginine-glycine-aspartic acid (RGD) peptide sequences exist in a variety of biological extracellular matrices and can specifically bind the cell-surface integrin alphavbeta3, which is overexpressed in cancer cells and plays important roles in tumor growth and invasion. Quantum dots (QDs) have been applied in the field of cell biology and can be physically conjugated to the surface of cancer cells for imaging. In this research, we developed QDs-RGD nanoparticles and investigated its application in pancreatic cancer cell imaging and its influence on the biological behavior of pancreatic cancer cells. The results of flow cytometric analysis showed that the alphavbeta3 receptor was markedly overexpressed on pancreatic cancer cells. In cellular uptake studies, the fluorescence signal of QDs-RGD nanoparticles in pancreatic cancer cells was higher than that of QDs without RGD conjugation, as determined by an inverted fluorescence microscope. Furthermore, the biological behavior of pancreatic cancer cells was affected by QDs-RGD nanoparticles, which inhibited proliferation, migration and invasion and induced G2-phase cell cycle arrest. With integrin alphavbeta3 as a target, QDs-RGD nanoparticles can generate high-quality images of pancreatic cancer cells and have immense potential for use in the targeted diagnosis and therapy of pancreatic cancer.

Shim, Y. and J. M. Song (2015). "Quantum dot nanoprobe-based high-content monitoring of notch pathway inhibition of breast cancer stem cell by capsaicin." Mol Cell Probes **29**(6): 376-381.

Breast cancer is the major cause of cancer death for women worldwide. Breast cancer patients are treated with chemotherapy and radiotherapy. Although chemotherapy and radiotherapy are applied, some cancer cells still survive. These cells, called cancer stem cell (CSC), exhibit special capabilities, such as drug and radio resistance. The remaining CSC can trigger cancer recurrence. Thus, it is critical to find an effective way to target CSC. Capsaicin has been reported to affect anticancer activity in many cancers. It also has been shown that capsaicin induces apoptosis in the MCF-7 breast cancer cell line. In this study, we demonstrate that capsaicin causes dose-dependent growth disruption in breast CSC and inhibits translocation of notch intracellular membrane domain (NICD) into the nucleus. MCF-7 cells were treated with capsaicin at various concentrations (5 muM, 10 muM, and 20 muM) for 24 h. After capsaicin treatment, it was found that the number of breast CSC (%) decreased as the treatment concentration of capsaicin increased. This result was also confirmed with FACS. NICD translocation to the nucleus and apoptotic cell death of breast CSC were concurrently observed at the single breast CSC level using highly sensitive quantum dot (Qdot)-antibody nanoprobes. The control breast CSCs without the capsaicin treatment were able to translocate NICD into the nucleus. On the other hand, translocation of NICD into the nucleus was not observed in capsaicin-treated cells. In addition, apoptotic cell death was caused when the breast CSC were treated with capsaicin at more than 10 muM. Although many studies have shown that capsaicin produces anticancer activity in cancer cell lines, the present result is the first report to demonstrate that capsaicin is capable of causing breast CSC apoptotic cell death via inhibiting its notch signaling pathway.

Shim, Y. and J. M. Song (2015). "Spectral overlap-free quantum dot-based determination of benzo[a]pyrene-induced cancer stem cells by concurrent monitoring of CD44, CD24 and aldehyde dehydrogenase 1." Chem Commun (Camb) **51**(11): 2118-2121.

In this study, it was found that breast cancer stem cells (CSCs) are formed from MCF-7 cells by benzo[a]pyrene (BP)-induced mutation. The breast CSCs were detected through simultaneous monitoring of CD44, CD24 and aldehyde dehydrogenase 1 (ALDH1) by hypermulticolor cellular imaging using an acousto-optical tunable filter (AOTF) and quantum dots (Q-dots).

Shojaeian, S., et al. (2018). "Quantum Dot-labeled Tags Improve Minimal Detection Limit of CA125 in Ovarian Cancer Cells and Tissues." Iran J Allergy Asthma Immunol **17**(4): 326-335.

In recent years, a lot of attention has been paid to quantum dot (QD) nanoparticles as fluorescent sensors for sensitive and accurate detection of cancer biomarkers. Here, using a homemade specific

monoclonal antibody against CA125 and QD525- or FITC-labeled probes, expression of this marker in an ovarian cancer cell line and cancer tissues were traced and optical properties of fluorophores were compared qualitatively and quantitatively. Our results clearly showed that besides lower background and exceptionally higher photobleaching resistance, QD525 exhibited higher fluorescent intensity for both ovarian cancer cell and tissues at different exposure times ($p<0.0001$) and excitation filter sets ($p<0.0001$) exemplified by significantly higher staining index ($p<0.016$). More importantly, the FITC-labeled probe detected antigen-antibody complex at minimum concentration of 0.3 mg/mL of anti-CA125, while reactivity limit decreased to 0.078 mg/mL of anti-CA125 when QD525-labeled probe was applied showing four times higher reactivity level of QD525 probe compared to the same probe labeled with FITC. Based on our results, it seems that QDs are inimitable tags for sensitive detection and localization of ovarian cancer micrometastasis and molecular demarcation of cancer tissues in surgical practice, which subsequently figure out accurate therapeutic approaches.

Shuang, W., et al. (2015). "Facile and controlled synthesis of stable water-soluble cupric sulfide quantum dots for significantly inhibiting the proliferation of cancer cells." J Mater Chem B **3**(27): 5603-5607.

Amorphous and crystalline copper sulfide quantum dots (QDs) with good water-solubility were obtained controllably by a novel hydrolysis strategy. These QDs exhibited anti-proliferation activities on cancer cells rather than normal cells and the biological activities are related to their polymorphs. Our study opens up new avenues for fabricating stable water-soluble metal sulfide QDs.

Singh, B. R., et al. (2012). "ROS-mediated apoptotic cell death in prostate cancer LNCaP cells induced by biosurfactant stabilized CdS quantum dots." Biomaterials **33**(23): 5753-5767.

Cadmium sulfide (CdS) quantum dots (QDs) have raised great attention because of their superior optical properties and wide utilization in biological and biomedical studies. However, little is known about the cell death mechanisms of CdS QDs in human cancer cells. This study was designed to investigate the possible mechanisms of apoptosis induced by biosurfactant stabilized CdS QDs (denoted as "bsCdS QDs") in human prostate cancer LNCaP cells. It was also noteworthy that apoptosis correlated with reactive oxygen species (ROS) production, mitochondrial damage, oxidative stress and chromatin condensation in a dose- and time-dependent manner. Results also showed involvement of caspases, Bcl-2 family proteins, heat shock protein 70, and a cell-cycle checkpoint protein p53 in apoptosis induction by bsCdS QDs in LNCaP cells. Moreover, pro-apoptotic protein Bax was upregulated and the anti-apoptotic proteins, survivin and NF-kappaB were downregulated in bsCdS QDs exposed cells. Protection of N-acetyl cysteine (NAC) against ROS clearly suggested the implication of ROS in hyper-activation of apoptosis and cell death. It is encouraging to conclude that biologically stabilized CdS QDs bear the potential of its applications in biomedicine, such as tumor therapy specifically by inducing caspase-dependent apoptotic cell death of human prostate cancer LNCaP cells.

Singh, G., et al. (2015). "Cancer Cell Targeting Using Folic Acid/Anti-HER2 Antibody Conjugated Fluorescent CdSe/CdS/ZnS-MPA and CdTe-MSA Quantum Dots." J Nanosci Nanotechnol **15**(12): 9382-9395.

CdSe/CdS/ZnS and CdTe quantum dots (QDs) were synthesized by successive ion layer adsorption and reaction (SILAR) technique and direct aqueous synthesis respectively using thiol stabilizers. Synthesized CdSe/CdS/ZnS and CdTe QDs stabilized with 3-mercaptopropionic acid (MPA) and mercaptosuccinic acid (MSA) were used as fluorescent labels after conjugation with folic acid (FA) and anti-HER2 antibodies. Photoluminescence quantum yield of folated CdSe/CdS/ZnS-MPA and CdTe-MSA QDs was 59% and 77% than that of non-folated hydrophilic QDs. The folate receptor-mediated delivery of folic acid-conjugated CdTe-MSA and CdSe/CdS/ZnS-MPA QDs showed higher cellular internalization as observed by confocal laser scanning microscopic studies. Folated and non-folated CdTe-MSA QDs were highly toxic and exhibited only 10% cell viability as compared to > 80% cell viability with CdSe/CdS/ZnS-MPA QDs over the concentration ranging from 3.38 to 50 pmoles. Immunohistochemistry (IHC) results of human breast cancer tissue samples showed positive results with anti-HER2 antibody conjugated CdSe/CdS/ZnS-MPA QDs with better sensitivity and specificity as compared to conventional IHC analysis using diaminobenzedene staining.

Singh, G., et al. (2016). "Cancer Cell Targeting Using Folic Acid/Anti-HER2 Antibody Conjugated Fluorescent CdSe/CdS/ZnS-Mercaptopropionic Acid and CdTe-Mercaptosuccinic Acid Quantum Dots." J Nanosci Nanotechnol **16**(1): 130-143.

CdSe/CdS/ZnS and CdTe quantum dots (QDs) were synthesized by successive ion layer adsorption and reaction (SILAR) technique and direct aqueous synthesis respectively using thiol stabilizers. Synthesized CdSe/CdS/ZnS and CdTe QDs stabilized with 3-mercaptopropionic acid (MPA) and mercaptosuccinic acid (MSA) were used as fluorescent labels after conjugation with folic acid (FA) and anti-

HER2 antibodies. Photoluminescence quantum yield of folated CdSe/CdS/ZnS-MPA and CdTe-MSA QDs was 59% and 77% than that of non-folated hydrophilic QDs. The folate receptor-mediated delivery of folic acid-conjugated CdTe-MSA and CdSe/CdS/ZnS-MPA QDs showed higher cellular internalization as observed by confocal laser scanning microscopic studies. Folated and non-folated CdTe-MSA QDs were highly toxic and exhibited only 10% cell viability as compared to > 80% cell viability with CdSe/CdS/ZnS-MPA QDs over the concentration ranging from 3.38 to 50 pmoles. Immunohistochemistry (IHC) results of human breast cancer tissue samples showed positive results with anti-HER2 antibody conjugated CdSe/CdS/ZnS-MPA QDs with better sensitivity and specificity as compared to conventional IHC analysis using diaminobenzedene staining.

Singh, S., et al. (2016). "A quantum dot-MUC1 aptamer conjugate for targeted delivery of protoporphyrin IX and specific photokilling of cancer cells through ROS generation." Integr Biol (Camb) **8**(10): 1040-1048.

Non-targeted photosensitizers lack selectivity that undermines the potential use of photodynamic therapy (PDT). Herein, we report the DNA mediated assembly of a ZnSe/ZnS quantum dot (QD)-photosensitizer (PS)-Mucin 1(MUC1) aptamer conjugate for targeting the MUC1 cancer biomarker and simultaneous generation of reactive oxygen species (ROS). A photosensitizer, protoporphyrin IX (PpIX), was conjugated to a single stranded DNA and self-assembled to a complementary strand that was conjugated to a QD and harboring a MUC1 aptamer sequence. A multistep fluorescence resonance energy transfer (FRET) is shown that involves the QD, PpIX and covalently linked CF 633 amine dye (CF dye) to the MUC1 peptide that tracks the potency of the aptamer to attach itself with the MUC1 peptide. Since the absorption spectra of the CF dye overlap with the emission spectra of PpIX, the former acts as an acceptor to PpIX forming a second FRET pair when the dye labeled MUC1 binds to the aptamer. The binding of the QD-PpIX nanoassemblies with MUC1 through the aptamer was further confirmed by gel electrophoresis and circular dichroism studies. The selective photodamage of MUC1 expressing HeLa cervical cancer cells through ROS generation in the presence of the QD-PpIX FRET probe upon irradiation is successfully demonstrated.

Singh, S. P. (2011). "Multifunctional magnetic quantum dots for cancer theranostics." J Biomed Nanotechnol **7**(1): 95-97.

The development of an innovative platform for cancer theranostics that will be capable of noninvasive imaging and treatment of cancerous tumors using biocompatible and multifunctional Fe3O4-ZnO core-shell magnetic quantum dots (M-QDs) is being explored. This multi-functional approach will facilitate deep tumor targeting using a combination of a specific cancer marker and an external magnetic field will simultaneously provide therapy that may evolve as a new paradigm in cancer theranostics.

Smith, A. M., et al. (2006). "Multicolor quantum dots for molecular diagnostics of cancer." Expert Rev Mol Diagn **6**(2): 231-244.

In the pursuit of sensitive and quantitative methods to detect and diagnose cancer, nanotechnology has been identified as a field of great promise. Semiconductor quantum dots are nanoparticles with intense, stable fluorescence, and could enable the detection of tens to hundreds of cancer biomarkers in blood assays, on cancer tissue biopsies, or as contrast agents for medical imaging. With the emergence of gene and protein profiling and microarray technology, high-throughput screening of biomarkers has generated databases of genomic and expression data for certain cancer types, and has identified new cancer-specific markers. Quantum dots have the potential to expand this in vitro analysis, and extend it to cellular, tissue and whole-body multiplexed cancer biomarker imaging.

Smith, C. I., et al. (2018). "Application of a quantum cascade laser aperture scanning near-field optical microscope to the study of a cancer cell." Analyst **143**(24): 5912-5917.

This work reports the first images obtained by combining an infrared aperture scanning near-field optical microscope (SNOM) with a quantum cascade laser (QCL). The future potential of this set-up is demonstrated by a preliminary study on an OE33 human oesophageal adenocarcinoma cell in which the cell is imaged at 1751 cm-1, 1651 cm-1, 1539 cm-1 and 1242 cm-1. In addition to the 1651 cm-1 image, three other images were acquired within the Amide I band (1689 cm-1, 1675 cm-1 and 1626 cm-1) chosen to correspond to secondary structures of proteins. The four images obtained within the Amide I band show distinct differences demonstrating the potential of this approach to reveal subtle changes in the chemical composition of a cell.

Soleymani, J., et al. (2018). "Targeting and sensing of some cancer cells using folate bioreceptor functionalized nitrogen-doped graphene quantum dots." Int J Biol Macromol **118**(Pt A): 1021-1034.

In recent years, study of folate receptor (FR) expression related to targeting, drug delivery and counting of tumoral cells have been followed. In this work, a fast and simple strategy was reported to determine the FR expressed cancer cells based on the

selective bonding of the folic acid/folate (FA) to the FR-positive tumor cells. The folate decorated Nitrogen-doped graphene quantum dots (N-GQDs) were utilized as selective targeting of the MKN 45 cells. Fluorescent microscopy imaging investigations revealed that the produced FA conjugated N-GQDs could specifically attach to the target FR-positive tumor cells. Due to the fluorescence emission of N-GQDs, the developed cytosensor is free from attaching any fluorescent ligand i.e. Rhodamine B to capture the florescence microscopy images and also flow cytometry analysis. The fabricated cytosensor possesses a dynamic range from 100 to 7.0x10(4)cell.mL(-1) with high selectivity. Furthermore, the cytosensor also could visualized the MCF 7 and HT 29 cells where the dynamic ranges were 100 to 1.0x10(4) and 500 to 4.0x10(4)cells.mL(-1), respectively. In vitro toxicity tests has shown low toxicity of the synthesized N-GQDs where the minimum viability is 68%. The proposed FA-N-GQDs based cytosensor provides a novel platform for detection of MKN 45, HT 29 and MCF 7 cancer cell lines which could be used in multi-channel cancer diagnosis biodevice.

Song, H., et al. (2022). "Biologically Safe, Versatile, and Smart Bismuthene Functionalized with a Drug Delivery System Based on Red Phosphorus Quantum Dots for Cancer Theranostics." Angew Chem Int Ed Engl **61**(22): e202117679.

Two-dimensional nanomaterials are attracting attention for cancer therapy. However, high toxicity, insensitivity to external stimuli and single therapeutic modality are still key issues hindering their clinical application. Therefore, the construction of a safe, intelligent and versatile nanocomposite is needed to meet clinical expectations. Herein, we developed a nanocomposite of Bi@RP-PEG-DOX with 2D bismuthene loaded with 0D red phosphorus quantum dots and DOX. The nanocomposite with DOX loading capacity (ca. 250 %) and photothermal conversion efficiency (ca. 54 %) showed both photothermal and photodynamic effects and a sensitive response of drug release to the acidic tumor microenvironment or NIR II laser irradiation. The nanocomposite exhibits good biosafety. Through the X-ray attenuation properties of bismuth, the nanocomposite serves as an excellent CT contrast agent, providing potential to perform CT-guided therapy.

Sukhanova, A., et al. (2021). "Multiphoton Deep-Tissue Imaging of Micrometastases and Disseminated Cancer Cells Using Conjugates of Quantum Dots and Single-Domain Antibodies." Methods Mol Biol **2350**: 105-123.

Early detection of malignant tumors, micrometastases, and disseminated tumor cells is one of the effective way of fighting cancer. Among the many existing imaging methods like computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), optical imaging with fluorescent probes is one of the most promising alternatives because it is fast, inexpensive, safe, sensitive, and specific. However, traditional fluorescent probes, based on organic fluorescent dyes, suffer from the low signal-to-noise ratio. Furthermore, conventional organic fluorescent dyes are unsuitable for deep tissue imaging because of the strong visible light absorption by biological tissues. The use of fluorescent semiconductor nanocrystals, or quantum dots (QDs), may overcome this limitation due to their large multiphoton cross section, which ensures efficient imaging of thick tissue sections inaccessible with conventional fluorescent probes. Moreover, the lower photobleaching and higher brightness of fluorescence signals from QDs ensures a much better discrimination of positive signals from the background. The use of fluorescent nanoprobes based on QDs conjugated to uniformly oriented high-affinity single-domain antibodies (sdAbs) may significantly increase the sensitivity and specificity due to better recognition of analytes and deeper penetration into tissues due to small size of such nanoprobes.Here, we describe a protocol for the fabrication of nanoprobes based on sdAbs and QDs, preparation of experimental xenograft mouse models for quality control, and multiphoton imaging of deep-tissue solid tumors, micrometastases, and disseminated tumor cells.

Sun, G., et al. (2018). "Targeting breast cancer cells with a CuInS2/ZnS quantum dot-labeled Ki-67 bioprobe." Oncol Lett **15**(2): 2471-2476.

The aim of the present study was to develop a water-soluble biomarker for the detection of breast cancer using quantum dots (QDs) conjugated to Ki-67, a nuclear protein associated with the cell cycle. Ki-67 is also a marker of cell proliferation, with expression levels categorizing good and poor prognosis in invasive breast cancer. Ki-67 is a clinically used biomarker for breast cancer diagnosis, treatment and prognosis. Owing to the optical and chemical advantages of QDs, QD-based nanotechnology may aid the construction of a biomedical imaging platform for the study of cancer cell behavior. In the present study, a biomarker was prepared by employing the water-soluble CuInS2/ZnS QDs conjugated to an anti-Ki-67 monoclonal antibody to detect Ki-67 expression in breast cancer. The QDs, which were hydrophobic and coated with octadecylamine, were encapsulated with an amphiphilic biocompatible centipede-like polymer, and then conjugated to anti-Ki-67 monoclonal antibodies (QD-Ki-67 probes). The QD-Ki-67 probes retained the original optical properties of the unadorned QDs and did

not exhibit distinct toxic side effects in in vitro cytotoxicity experiments. Therefore, this CuInS2/ZnS QD-labeled bioprobe, with a high quantum yield and low cytotoxicity, is a promising candidate for bioimaging and may be used as a cell label.

Sun, J. Z., et al. (2014). "Quantum dot-based immunofluorescent imaging of Ki67 and identification of prognostic value in HER2-positive (non-luminal) breast cancer." Int J Nanomedicine **9**: 1339-1346.

BACKGROUND: The immunohistochemical assessment of Ki67 antigen (Ki67) is the most widely practiced measurement of breast cancer cell proliferation; however, it has some disadvantages and thus the prognostic value of Ki67 in breast cancer remains controversial. Our previous studies confirmed the advantages of quantum dots-based nanotechnology for quantitative analysis of biomarkers compared with conventional immunohistochemistry (IHC). This study was designed to assess Ki67 by quantum dot-immunohistochemistry (QD-IHC) and investigate the prognostic value of the Ki67 score in human epidermal growth factor receptor 2 (HER2)-positive (non-luminal) breast cancer. METHODS: Ki67 expression in 108 HER2-positive (non-luminal) breast cancer specimens was detected by IHC and QD-IHC. Two observers assessed the Ki67 score independently and comparisons between the two methods were made. The prognostic value of the Ki67 score for five-year disease-free survival was estimated. RESULTS: The same antigen localization, high correlation of staining rates (r=0.993), and high agreement of measurements (kappa=0.874) of Ki67 expression (cutoff: 30%) in breast cancer were found by QD-IHC and conventional IHC. The QD-IHC had a better interobserver agreement for the Ki67 score than conventional IHC (t=-7.280, P<0.01). High Ki67 expression (cutoff: 30%) was associated with shorter disease-free survival (log-rank test; IHC, P=0.026; QD-IHC, P=0.001), especially in the lymph node-negative subgroups (log-rank test; IHC, P=0.017; QD-IHC, P=0.002). CONCLUSION: QD-IHC imaging of Ki67 was an easier and more accurate method for detecting and assessing Ki67. The Ki67 score was an independent prognosticator in the HER2-positive (non-luminal) breast cancer patients.

Sun, M. F., et al. (2019). "Three-Dimensional Cadmium Telluride Quantum Dots-DNA Nanoreticulation as a Highly Efficient Electrochemiluminescent Emitter for Ultrasensitive Detection of MicroRNA from Cancer Cells." Anal Chem **91**(12): 7765-7773.

In this work, a novel three-dimensional cadmium telluride quantum dots-DNA nanoreticulation (3D CdTe QDs-DNA-NR) was used as a signal probe with the dual-legged DNA walker circular amplification as target conversion strategy to establish a pioneering electrochemiluminescence (ECL) biosensing strategy for ultrasensitive detection of microRNA-21 form cancer cells. Herein, such a 3D luminous nanomaterial with reticular structure not only supported abundant CdTe QDs to avoid the inner filter effect for obtaining a high ECL efficiency but also contained the hemin/G-quadruplex as coreaction accelerator in the 3D CdTe QDs-DNA-NR/S2O8(2-) system for the enhancement of ECL intensity. Furthermore, with the target-induced dual-legged DNA walker circular amplification strategy, a mass of output DNA was produced to connect with the 3D CdTe QDs-DNA-NR for the construction of the ECL biosensor, which realized the ultrasensitive detection of microRNA-21 from 100 aM to 100 pM and the detection limit down to 34 aM. Significantly, this work could be readily extended for the detection of other biomolecules to provide a neoteric channel for disease diagnosis.

Sun, X., et al. (2014). "Synthesis and application of a targeting diagnosis system via quantum dots coated by amphiphilic polymer for the detection of liver cancer cells." Luminescence **29**(7): 831-836.

Water-soluble quantum dots (QDs) for liver cancer diagnosis were prepared using QDs with oleylamine ligand coated with poly(aspartate)-graft-poly(ethylene glycol)-dodecylamine (PASP-Na-g-PEG-DDA). Dynamic light scattering and transmission electron microscopy imaging showed that the novel QDs have an ellipsoidal morphology with a size of ~ 45 nm which could be used for biomedical application. Furthermore, the PASP-Na-g-PEG-DDA was then modified with anti-(vascular endothelial growth factor) (VEGF antibody), and a 1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan (MTT) assay showed that the novel anti-VEGF-targeting QDs in vitro had low toxicity. Confocal laser scanning microscopy observations revealed an intracellular (HepG2) distribution of the novel anti-VEGF-targeting QDs and the targeting efficiency of anti-VEGF. These novel QDs could be used as a probe for liver cancer cell imaging because of anti-VEGF targeting.

Sun, Y., et al. (2020). "MicroRNA-mediated suppression of P-glycoprotein by quantum dots in lung cancer cells." J Appl Toxicol **40**(4): 525-534.

The interactions between adenosine triphosphate-binding cassette (ABC) transporters and nano-sized materials are attracting increasing attention, due to their great potential in overcoming the multidrug resistance (MDR) phenomena in cancer treatment. However, the inner mechanisms involved in the interactions are largely unknown. In this study, two commercial quantum dots (QDs), CdSe/ZnS-MPA and CdSe/ZnS-GSH, were tested for their interactions with P-glycoprotein (P-gp), as well as the relating

mechanisms in lung cancer (A549) cells. Both QDs significantly suppressed the gene and protein expressions of P-gp in A549 cells. To explain this, the gene expressions of nine relating microRNAs (miRNAs) were evaluated. The results indicated a shared up-regulation of miR-34b and miR-185 by both QDs. Furthermore, mimics and inhibitors of miR-34b and miR-185 significantly enhanced and suppressed the gene and protein expressions of P-gp, respectively, confirming the modulatory function of these two miRNAs on P-gp. Interestingly, expressions of both miRNAs were suppressed during treatment with Cd(2+) and doxorubicin, which induced the expression of P-gp, indicating the universality of these miRNAs-related mechanisms. Thus, as miR-34b and miR-185 participated in the suppression of P-gp functions in A549 cells they could be interesting targets for the treatment of lung cancer.

Sun, Z., et al. (2017). "TiL4 -Coordinated Black Phosphorus Quantum Dots as an Efficient Contrast Agent for In Vivo Photoacoustic Imaging of Cancer." Small **13**(11).

Black phosphorus quantum dots coordinated with a sulfonic ester of the titanium ligand are prepared and exhibit enhanced stability. In vitro and in vivo photoacoustic imaging applications demonstrate that the quantum dots can efficiently accumulate inside the tumor producing tumor profiles with high spatial resolution, demonstrating their potential as an efficient agent for photoacoustic imaging.

Sung, Y. M., et al. (2015). "Quinone-Modified Mn-Doped ZnS Quantum Dots for Room-Temperature Phosphorescence Sensing of Human Cancer Cells That Overexpress NQO1." ACS Appl Mater Interfaces **7**(46): 25961-25969.

Early detection of cancer cells in a rapid and sensitive approach is one of the great challenges in modern clinical cancer care. This study has demonstrated the first example of a rapid, selective, and sensitive phosphorescence probe based on phosphorescence energy transfer (PET) for cancer-associated human NAD(P)H: quinone oxidoreductase isozyme 1 (NQO1). An efficient room-temperature phosphorescence NQO1 probe was constructed by using Mn-doped ZnS quantum dots (Mn:ZnS QDs) as donors and trimethylquinone propionic acids as acceptors. Phosphorescence quenching of Mn:ZnS QDs from the Mn:ZnS QDs to a covalently bonded quinone was achieved through PET. Phosphorescence of Mn:ZnS QDs was turned on by the rapid reduction-initiated removal of the quinone quencher by NQO1. This probe shows low cellular toxicity and can rapidly distinguish between NQO1-expressing and -nonexpressing cancer cell lines through phosphorescence imaging.

Suriamoorthy, P., et al. (2010). "Folic acid-CdTe quantum dot conjugates and their applications for cancer cell targeting." Cancer Nanotechnol **1**(1-6): 19-28.

In this study, we report the preparation, luminescence, and targeting properties of folic acid-CdTe quantum dot conjugates. Water-soluble CdTe quantum dots were synthesized and conjugated with folic acid using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide-N-hydroxysuccinimide chemistry. The influence of folic acid on the luminescence properties of CdTe quantum dots was investigated, and no energy transfer between them was observed. To investigate the efficiency of folic acid-CdTe nanoconjugates for tumor targeting, pure CdTe quantum dots and folic acid-coated CdTe quantum dots were incubated with human nasopharyngeal epidermal carcinoma cell line with positive expressing folic acid receptors (KB cells) and lung cancer cells without expression of folic acid receptors (A549 cells). For the cancer cells with positive folate receptors (KB cells), the uptake for CdTe quantum dots is very low, but for folic acid-CdTe nanoconjugates, the uptake is very high. For the lung cancer cells without folate receptors (A549 cells), the uptake for folic acid-CdTe nanoconjugates is also very low. The results indicate that folic acid is an effective targeting molecule for tumor cells with overexpressed folate receptors.

Tabatabaei-Panah, A. S., et al. (2013). "Accurate sensitivity of quantum dots for detection of HER2 expression in breast cancer cells and tissues." J Fluoresc **23**(2): 293-302.

Here we introduce novel optical properties and accurate sensitivity of Quantum dot (QD)-based detection system for tracking the breast cancer marker, HER2. QD525 was used to detect HER2 using home-made HER2-specific monoclonal antibodies in fixed and living HER2(+) SKBR-3 cell line and breast cancer tissues. Additionally, we compared fluorescence intensity (FI), photostability and staining index (SI) of QD525 signals at different exposure times and two excitation wavelengths with those of the conventional organic dye, FITC. Labeling signals of QD525 in both fixed and living breast cancer cells and tissue preparations were found to be significantly higher than those of FITC at 460-495 nm excitation wavelengths. Interestingly, when excited at 330-385 nm, the superiority of QD525 was more highlighted with at least 4-5 fold higher FI and SI compared to FITC. Moreover, QDs exhibited exceptional photostability during continuous illumination of cancerous cells and tissues, while FITC signal faded very quickly. QDs can be used as sensitive reporters for in situ detection of tumor markers which in turn could be viewed as a novel approach for early detection of cancers. To take

comprehensive advantage of QDs, it is necessary that their optimal excitation wavelength is employed.

Tade, R. S., et al. (2022). "Graphene quantum dots (GQDs) nanoarchitectonics for theranostic application in lung cancer." J Drug Target **30**(3): 269-286.

Lung cancer (LC) is heading up as a substantial cause of mortality worldwide. Despite enormous progress in cancer management, LC remains a crucial problem for oncologists due to the lack of early diagnosis and precise treatment. In this context, numerous early diagnosis and treatment approaches for LC at the cellular level have been developed using advanced nanomaterials in the last decades. Amongst this, graphene quantum dots (GQDs) as a novel fluorescent material overwhelmed the horizons of materials science and biomedical fields due to their multifunctional attributes. Considering the complex nature of LC, emerging diagnostic and therapeutic (Theranostics) strategies using GQDs proved to be an effective way for the current practice in LC. In this line, we have abridged various approaches used in the LC theranostics using GQDs and its surface-engineered motif. The admirable photophysical attributes of GQDs realised in photolytic therapy (PLT), hyperthermia therapy (HTT), and drug delivery have been discussed. Furthermore, we have engrossed the impasse and its effects on the use of GQDs in cancer treatments from cellular level (in vivo-in vitro) to clinical. Inclusively, this review will be an embodiment for the scientific fraternity to design and magnify their view for the theranostic application of GQDs in LC treatment.

Tade, R. S. and P. O. Patil (2020). "Theranostic Prospects of Graphene Quantum Dots in Breast Cancer." ACS Biomater Sci Eng **6**(11): 5987-6008.

Breast cancer (BC) is increasing as a significant cause of mortality among women. In this context, early diagnosis and treatment strategies for BC are being developed by researchers at the cellular level using advanced nanomaterials. However, immaculate etiquette is the prerequisite for their implementation in clinical practice. Considering the stolid nature of cancer, combining diagnosis and therapy (theranostics) using graphene quantum dots (GQDs) is a prime focus and challenge for researchers. In a nutshell, GQDs is a new shining star among various fluorescent materials, which has acclaimed fame in a short duration in materials science and the biomedical field as well. From this perspective, we review various strategies in BC treatment using GQDs alone or in combination. In addition, the photophysical properties of GQDs explored in photothermal therapy, hyperthermia therapy, and photodynamic therapy are also discussed. Moreover, we also focus on the strategic use of GQDs both as drug carriers and as combinatorial-guided drug delivery motifs. This Review provides an update for the scientific community to plan and expand advanced theranostic horizons in BC using GQDs.

Tandale, P., et al. (2021). "Fluorescent quantum dots: An insight on synthesis and potential biological application as drug carrier in cancer." Biochem Biophys Rep **26**: 100962.

Quantum dots (QDs) are nanocrystals of semiconducting material possessing quantum mechanical characteristics with capability to get conjugated with drug moieties. The particle size of QDs varies from 2 to 10 nm and can radiate a wide range of colours depending upon their size. Their wide and diverse usage of QDs across the world is due to their adaptable properties like large quantum yield, photostability, and adjustable emission spectrum. QDs are nanomaterials with inherent electrical characteristics that can be used as drug carrier vehicle and as a diagnostic in the field of nanomedicine. Scientists from various fields are aggressively working for the development of single platform that can sense, can produce a microscopic image and even be used to deliver a therapeutic agent. QDs are the fluorescent nano dots with which the possibilities of the drug delivery to a targeted site and its biomedical imaging can be explored. This review is mainly focused on the different process of synthesis of QDs, their application especially in the areas of malignancies and as a theranostic tool. The attempt is to consolidate the data available for the use of QDs in the biomedical applications.

Tang, R., et al. (2015). "Tunable ultrasmall visible-to-extended near-infrared emitting silver sulfide quantum dots for integrin-targeted cancer imaging." ACS Nano **9**(1): 220-230.

The large size of many near-infrared (NIR) fluorescent nanoparticles prevents rapid extravasation from blood vessels and subsequent diffusion to tumors. This confines in vivo uptake to the peritumoral space and results in high liver retention. In this study, we developed a viscosity modulated approach to synthesize ultrasmall silver sulfide quantum dots (QDs) with distinct tunable light emission from 500 to 1200 nm and a QD core diameter between 1.5 and 9 nm. Conjugation of a tumor-avid cyclic pentapeptide (Arg-Gly-Asp-DPhe-Lys) resulted in monodisperse, water-soluble QDs (hydrodynamic diameter < 10 nm) without loss of the peptide's high binding affinity to tumor-associated integrins (KI = 1.8 nM/peptide). Fluorescence and electron microscopy showed that selective integrin-mediated internalization was observed only in cancer cells treated with the peptide-labeled QDs, demonstrating that the unlabeled hydrophilic nanoparticles exhibit characteristics of negatively charged fluorescent dye molecules, which typically do

not internalize in cells. The biodistribution profiles of intravenously administered QDs in different mouse models of cancer reveal an exceptionally high tumor-to-liver uptake ratio, suggesting that the small sized QDs evaded conventional opsonization and subsequent high uptake in the liver and spleen. The seamless tunability of the QDs over a wide spectral range with only a small increase in size, as well as the ease of labeling the bright and noncytotoxic QDs with biomolecules, provides a platform for multiplexing information, tracking the trafficking of single molecules in cells, and selectively targeting disease biomarkers in living organisms without premature QD opsonization in circulating blood.

Tao, J., et al. (2021). "Hyaluronic acid conjugated nitrogen-doped graphene quantum dots for identification of human breast cancer cells." Biomed Mater **16**(5).

Accurate distinguish of cancer cells through fluorescence plays an important role in cancer diagnosis. Here we synthesized a blue fluorescent nitrogen-doped graphene quantum dots (N-GQDs) from citric acid and diethylamine via one-step hydrothermal synthesis method which was simple and quick to avoid by-products, and highlighted the binding sites to achieve precise combination. Due to the nitrogen element doping, amide II bond was amply obtained and abundant binding sites were provided for hyaluronic acid (HA) conjugation. N-GQDs solution with different pH value was then conjugated to HA via an amide bond for the recognition of human breast cancer cells (MCF-7 cells), and the formation of amide bond was more favorable under alkaline conditions. HA conjugated N-GQDs (HA-N-GQDs) were combined with CD44 which was over expressed on the surface of MCF-7 cells, resulting in MCF-7 cells performing stronger fluorescence. HA-N-GQDs showed high fluorescence, low toxicity, and good cytocompatibility, which held it play a role in fluorescence imaging for accurate identification of cancer cells.

Tao, W., et al. (2017). "Antimonene Quantum Dots: Synthesis and Application as Near-Infrared Photothermal Agents for Effective Cancer Therapy." Angew Chem Int Ed Engl **56**(39): 11896-11900.

Photothermal therapy (PTT) has shown significant potential for cancer therapy. However, developing nanomaterials (NMs)-based photothermal agents (PTAs) with satisfactory photothermal conversion efficacy (PTCE) and biocompatibility remains a key challenge. Herein, a new generation of PTAs based on two-dimensional (2D) antimonene quantum dots (AMQDs) was developed by a novel liquid exfoliation method. Surface modification of AMQDs with polyethylene glycol (PEG) significantly enhanced both biocompatibility and stability in physiological medium. The PEG-coated AMQDs showed a PTCE of 45.5 %, which is higher than many other NMs-based PTAs such as graphene, Au, MoS2 , and black phosphorus (BP). The AMQDs-based PTAs also exhibited a unique feature of NIR-induced rapid degradability. Through both in vitro and in vivo studies, the PEG-coated AMQDs demonstrated notable NIR-induced tumor ablation ability. This work is expected to expand the utility of 2D antimonene (AM) to biomedical applications through the development of an entirely novel PTA platform.

Thakur, M., et al. (2016). "Milk-derived multi-fluorescent graphene quantum dot-based cancer theranostic system." Mater Sci Eng C Mater Biol Appl **67**: 468-477.

An economical green-chemistry approach was used for the synthesis of aqueous soluble graphene quantum dots (GQDs) from cow milk for simultaneous imaging and drug delivery in cancer. The GQDs synthesized using one-pot microwave-assisted heating were multi-fluorescent, spherical in shape having a lateral size of ca. 5nm. The role of processing parameters such as heating time and ionic strength showed a profound effect on photoluminescence properties of GQDs. The GQDs were N-doped and oxygen-rich as confirmed by X-ray photoelectron spectroscopy (XPS) analysis. Cysteamine hydrochloride (Cys) was used to attach an anti-cancer drug berberine hydrochloride (BHC) on GQDs forming GQDs@Cys-BHC complex with c.a. 88% drug loading efficiency. In vitro drug release was studied at the acidic-basic environment and drug kinetics was studied using pharmacokinetic statistical models. The GQDs were biocompatible on L929 cells whereas theranostic GQDs@Cys-BHC complex showed a potent cytotoxic effect on different cancerous cell line models: cervical cancer cell lines such as HeLa cells and breast cancer cells such as MDA-MB-231 confirmed by Trypan blue and MTT-based cytotoxic assays. Furthermore, multi-excitation based cellular bioimaging was demonstrated using confocal laser scanning microscopy (CLSM) and fluorescence microscopy using GQDs as well as GQDs@Cys-BHC complex. Thus, drug delivery (therapeutic) and bioimaging (diagnostic) properties of GQDs@Cys-BHC complex are thought to have a potential in vitro theranostic application in cancer therapy.

Thomson, C. and J. R. Ball (1978). "Quantum chemical investigations of charge-transfer interactions in relation to the electronic theory of cancer." Ciba Found Symp(67): 143-164.

The results of ab initio 'supermolecule' calculations of the charge transfer between formamide

and methylglyoxal, dimethylglyoxal and ethylglyoxal are compared for several different relative conformations of the constituent molecules. The extent and sign of the charge transfer is similar for all three molecules; the ketoaldehyde acts as an electron acceptor only for the stacked conformation. Similar calculations on alpha-hydroxytetronic acid as a model for ascorbic acid show that it can act as either an acceptor from formamide or a donor to glyoxal.

Tiwari, D. K., et al. (2009). "Synthesis and Characterization of Anti-HER2 Antibody Conjugated CdSe/CdZnS Quantum Dots for Fluorescence Imaging of Breast Cancer Cells." Sensors (Basel) **9**(11): 9332-9364.

The early detection of HER2 (human epidermal growth factor receptor 2) status in breast cancer patients is very important for the effective implementation of anti-HER2 antibody therapy. Recently, HER2 detections using antibody conjugated quantum dots (QDs) have attracted much attention. QDs are a new class of fluorescent materials that have superior properties such as high brightness, high resistance to photo-bleaching, and multi-colored emission by a single-light source excitation. In this study, we synthesized three types of anti-HER2 antibody conjugated QDs (HER2Ab-QDs) using different coupling agents (EDC/sulfo-NHS, iminothiolane/sulfo-SMCC, and sulfo-SMCC). As water-soluble QDs for the conjugation of antibody, we used glutathione coated CdSe/CdZnS QDs (GSH-QDs) with fluorescence quantum yields of 0.23 approximately 0.39 in aqueous solution. Dispersibility, hydrodynamic size, and apparent molecular weights of the GSH-QDs and HER2Ab-QDs were characterized by using dynamic light scattering, fluorescence correlation spectroscopy, atomic force microscope, and size-exclusion HPLC. Fluorescence imaging of HER2 overexpressing cells (KPL-4 human breast cancer cell line) was performed by using HER2Ab-QDs as fluorescent probes. We found that the HER2Ab-QD prepared by using SMCC coupling with partially reduced antibody is a most effective probe for the detection of HER2 expression in KPL-4 cells. We have also studied the size dependency of HER2Ab-QDs (with green, orange, and red emission) on the fluorescence image of KPL-4 cells.

Toledo-Cortes, S., et al. (2022). "Grading diabetic retinopathy and prostate cancer diagnostic images with deep quantum ordinal regression." Comput Biol Med **145**: 105472.

Although for many diseases there is a progressive diagnosis scale, automatic analysis of grade-based medical images is quite often addressed as a binary classification problem, missing the finer distinction and intrinsic relation between the different possible stages or grades. Ordinal regression (or classification) considers the order of the values of the categorical labels and thus takes into account the order of grading scales used to assess the severity of different medical conditions. This paper presents a quantum-inspired deep probabilistic learning ordinal regression model for medical image diagnosis that takes advantage of the representational power of deep learning and the intrinsic ordinal information of disease stages. The method is evaluated on two different medical image analysis tasks: prostate cancer diagnosis and diabetic retinopathy grade estimation on eye fundus images. The experimental results show that the proposed method not only improves the diagnosis performance on the two tasks but also the interpretability of the results by quantifying the uncertainty of the predictions in comparison to conventional deep classification and regression architectures. The code and datasets are available at https://github.com/stoledoc/DQOR.

Tripathi, S. K., et al. (2015). "Quantum Dots and their Potential Role in Cancer Theranostics." Crit Rev Ther Drug Carrier Syst **32**(6): 461-502.

The emergence of cancer nanomedicine is the result of fruitful advances in the fields of nanotechnology, bioimaging, formulation development, and molecular biology. Quantum dots (QDs) are the luminescent nanocrystals (NCs) that provide a multifunctional platform for imaging the biosystems following controlled delivery of therapeutic drugs, proteins, peptides, oligonucleotides, and genes. These engineered fluorescent probes with integrated imaging and carrier functionalities have become excellent tools for molecular diagnostics and delivery of therapeutics molecules. Flexible surface chemistry, unique optical properties, high sensitivity, and multiplexing capabilities of QDs certainly make them a most promising tool for personalized medicine. This review focuses on state-of-art advances in synthesizing QDs and highlights the approaches used for functionalization of QDs with desired ligands for targeted carriage to specific sites. Discussed is the role of QDs in antitumor therapy through drug delivery and gene delivery and the recently emerged photodynamic therapy (PDT). We also endeavor to critically address the major impediments in the clinical development of these multifunctional nanoplatforms, with a special focus on plausible advancements for the near future.

Tsoy, T., et al. (2020). "Multiplexed Detection of Cancer Serum Antigens with a Quantum Dot-Based Lab-on-Bead System." Methods Mol Biol **2135**: 225-236.

A quantum dot (QD)-based lab-on-bead system is a unique tool for multiple analysis of cancer markers in human serum samples by using a flow cytometer. In terms of specificity and sensitivity, this method is

comparable with ELISA, the "gold standard" of serological in-clinic detection of single analytes. Fluorescent microspheres encoded with QDs have been used for the quantitative detection of free and total prostate-specific antigen in human serum samples. Developed multiplex assay demonstrates a clear discrimination between serum samples from control subjects and cancer patients. The proposed QD-based method is adaptable and makes it possible to develop numerous clinical tests with decreased duration and cost for early diagnosis of various diseases.

Tu, C. C., et al. (2016). "Silicon Quantum Dot Nanoparticles with Antifouling Coatings for Immunostaining on Live Cancer Cells." ACS Appl Mater Interfaces **8**(22): 13714-13723.

Fluorescent silicon quantum dots (SiQDs) have shown a great potential as antiphotobleaching, nontoxic and biodegradable labels for various in vitro and in vivo applications. However, fabricating SiQDs with high water-solubility and high photoluminescence quantum yield (PLQY) remains a challenge. Furthermore, for targeted imaging, their surface chemistry has to be capable of conjugating to antibodies, as well as sufficiently antifouling. Herein, antibody-conjugated SiQD nanoparticles (SiQD-NPs) with antifouling coatings composed of bovine serum albumin (BSA) and polyethylene glycol (PEG) are demonstrated for immunostaining on live cancer cells. The monodisperse SiQD-NPs of diameter about 130 nm are synthesized by a novel top-down method, including electrochemical etching, photochemical hydrosilylation, high energy ball milling, and "selective-etching" in HNO3 and HF. Subsequently, the BSA and PEG are covalently grafted on to the SiQD-NP surface through presynthesized chemical linkers, resulting in a stable, hydrophilic, and antifouling organic capping layer with isothiocyanates as the terminal functional groups for facile conjugation to the antibodies. The in vitro cell viability assay reveals that the BSA-coated SiQD-NPs had exceptional biocompatibility, with minimal cytotoxicity at concentration up to 1600 mug mL(-1). Under 365 nm excitation, the SiQD-NP colloid emits bright reddish photoluminescence with PLQY = 45-55% in organic solvent and 5-10% in aqueous buffer. Finally, through confocal fluorescent imaging and flow cytometry analysis, the anti-HER2 conjugated SiQD-NPs show obvious specific binding to the HER2-overexpressing SKOV3 cells and negligible nonspecific binding to the HER2-nonexpressing CHO cells. Under similar experimental conditions, the immunofluorescence results obtained with the SiQD-NPs are comparable to those using conventional fluorescein isothiocyanate (FITC).

Tung, F. I., et al. (2020). "One-stop radiotherapeutic targeting of primary and distant osteosarcoma to inhibit cancer progression and metastasis using 2DG-grafted graphene quantum dots." Nanoscale **12**(16): 8809-8818.

The application of radiotherapy (RT) to treat osteosarcoma (OS) has been limited, but this is starting to change as the ability to target radiation energy to niches improves. Furthermore, lung cancer from highly metastatic OS is a major cause of death, so it is critical to explore new strategies to tackle metastasis. In this study, we designed a nanoscale radiosensitizer by grafting 2-deoxy-d-glucose (2DG) onto graphene quantum dots (GQD) to achieve OS targeting and boost RT efficacy. Combining the use of 2DG-grafted GQDs (2DG-g-GQD) with RT produced a significant increase in oxidative stress response and DNA damage in the 143B OS cell line compared with RT alone. Moreover, 2DG-g-GQDs selectively associated with 143B cells, and demonstrated the inhibition of migration in a scratch assay. We also demonstrated remarkable improvement in their ability to inhibit tumour progression and lung metastasis in an OS xenograft mouse model. Our results show that the use of 2DG-g-GQDs as OS-targeting radiosensitizers improves their therapeutic outcome and exhibits potential for use in low-dose precision RT for OS.

Uthamacumaran, A. (2017). "A biophysical approach to cancer dynamics: Quantum chaos and energy turbulence." Biosystems **156-157**: 1-22.

Cancer is a term used to define a collective set of rapidly evolving cells with immortalized replication, altered epimetabolomes and patterns of longevity. Identifying a common signaling cascade to target all cancers has been a major obstacle in medicine. A quantum dynamic framework has been established to explain mutation theory, biological energy landscapes, cell communication patterns and the cancer interactome under the influence of quantum chaos. Quantum tunneling in mutagenesis, vacuum energy field dynamics, and cytoskeletal networks in tumor morphogenesis have revealed the applicability for description of cancer dynamics, which is discussed with a brief account of endogenous hallucinogens, bioelectromagnetism and water fluctuations. A holistic model of mathematical oncology has been provided to identify key signaling pathways required for the phenotypic reprogramming of cancer through an epigenetic landscape. The paper will also serve as a mathematical guide to understand the cancer interactome by interlinking theoretical and experimental oncology. A multi-dimensional model of quantum evolution by adaptive selection has been established for cancer biology.

Vahedi, N., et al. (2022). "Hyaluronic acid-graphene quantum dot nanocomposite: Potential target drug delivery and cancer cell imaging." Biotechnol Appl Biochem **69**(3): 1068-1079.

Nowadays, the use of nanoparticle-based drug delivery systems has received much more attention. In this regard, here, graphene quantum dots (GQD) were used as drug carriers as well as imaging agents for cancer cells. In order to optimize the dose of the drug and reduce its side effects for healthy cells, hyaluronic acid was decorated on the surface of GQD to target cancer cells. The morphology and size of the synthesized nanoparticles alone and conjugated with hyaluronic acid were investigated using scanning electron microscopy (SEM) and transmission electron microscopy (TEM); TEM images revealed a particles size of approximately 5.67 and approximately 8.69 nm, respectively. In the presence of 1-ethyl-3-[3(dimethylamino)propyl]carbodiimide hydrochloride/N-hydroxysuccinimide (EDC/NHS), hyaluronic acid was bounded to dopamine hydrochloride and was prepared to react with GQD. After synthesis of graphene quantum dot-hyaluronic acid nanocomposite, curcumin (CUR) as a drug model was loaded on the synthesized nanocarriers, and its loading percentage was measured. The results showed that 98.02% of the drug was loaded on the nanocarriers. Also, the conjugation of each agent on the nanocarrier was approved by photoluminescence spectroscopy, Fourier transform infrared spectroscopy (FTIR), and UV-visible absorption techniques, and the results showed that the reactions were performed correctly. The effect of GQD, graphene quantum dot-hyaluronic acid, CUR, graphene quantum dot-hyaluronic acid-CUR on the viability of HeLa and L929 cells was evaluated by the MTT test. The results showed that the synthesized nanocarrier is completely biocompatible, and the drug nanocarriers reduce HeLa cell viability significantly due to the mediation of hyaluronic acid-CD44 for drug cell uptake. Simultaneously with drug delivery, the other goal of these nanocarriers is to image cancer cells by emitting fluorescent light. Fluorescent microscopy showed that these nanocarriers were adsorbed on HeLa cells, unlike L929 cells.

Valarmathi, T., et al. (2021). "Spectroscopic, quantum chemical and molecular docking studies on 1-amino-5-chloroanthraquinone: A targeted drug therapy for thyroid cancer." Spectrochim Acta A Mol Biomol Spectrosc **255**: 119659.

The DFT studies of the 1-Amino-5-chloro-anthraquinone (ACAQ) molecule have been carried out with extensive and accurate investigations of detailed vibrational and spectroscopic investigations and validated by experimentally. The optimized molecular structure and harmonic resonance frequencies were computed based on DFT/B3LYP method with 6-311G++(d,p) basis set using the Gaussian 09 program. The experimental and calculated vibrational wavenumbers were assigned on the basis of PED calculations using VEDA 4.0 program. The (13)C NMR isotropic chemical shifts of the molecule were calculated using Gauge-Invariant-Atomic Orbital (GIAO) method in DMSO solution and compared with the experimental data. The absorption spectrum of the molecule was computed in liquid phase (ethanol), which exhibits small el, Cyrillic to small el, Cyrillic* electronic transition and compared with observed UV-Vis spectrum. Frontier molecular orbitals analysis shows the molecular reactivity and kinetic stability of the molecule. The Mulliken atomic charge distribution and molecular electrostatic potential surface analysis of the molecule validate the reactive site of the molecule. The natural bond orbital analysis proves the bioactivity of the molecule. Molecular docking analysis indicate that ACAQ molecule inhibits the action of c-Met Kinase protein, which is associated with the thyroid cancer. Hence, the present study pave the way for the development of novel drugs in the treatment of thyroid cancer.

Varnavski, O., et al. (2022). "Quantum Light-Enhanced Two-Photon Imaging of Breast Cancer Cells." J Phys Chem Lett **13**(12): 2772-2781.

Correct biological interpretation from cell imaging can be achieved only if the observed phenomena proceed with negligible perturbation from the imaging system. Herein, we demonstrate microscopic images of breast cancer cells created by the fluorescence selectively excited in the process of entangled two-photon absorption in a scanning microscope at an excitation intensity orders of magnitude lower than that used for classical two-photon microscopy. Quantum enhanced entangled two-photon microscopy has shown cell imaging capabilities at an unprecedented low excitation intensity of approximately 3.6 x 10(7) photons/s, which is a million times lower than the excitation level for the classical two-photon fluorescence image obtained in the same microscope. The extremely low light probe intensity demonstrated in entangled two-photon microscopy is of critical importance to minimize photobleaching during repetitive imaging and damage to cells in live-cell applications. This technology opens new avenues in cell investigations with light microscopy, such as enhanced selectivity and time-frequency resolution.

Vibin, M., et al. (2014). "Effective cellular internalization of silica-coated CdSe quantum dots for high contrast cancer imaging and labelling applications." Cancer Nanotechnol **5**(1): 1.

The possibility of developing novel contrast imaging agents for cancer cellular labelling and fluorescence imaging applications were explored using silica-coated cadmium selenide (CdSe) quantum dots (QDs). The time dependent cellular internalization efficiency study was carried out using Inductively Coupled Plasma-Optical Emission Spectroscopy (ICP-OES) and Confocal Laser Scanning Microscopy (cLSM) after exposing QDs to stem cells and cancer cells. The strong fluorescence from the cytoplasm confirmed that the QDs were efficiently internalized by the cells. The internalization maxima were observed at the fourth hour of incubation in both stem and cancer cells. Further, the in vitro fluorescence imaging as well as localization study of QDs were performed in various cells. Moreover, high contrast in vivo tumor imaging efficiency of silica-coated CdSe QDs was performed in ultrathin sections of tumor mice, and the results confirmed its effective role in cellular imaging and labelling in cancer and other diseases.

Vibin, M., et al. (2011). "Fluorescence imaging of stem cells, cancer cells and semi-thin sections of tissues using silica-coated CdSe quantum dots." J Fluoresc **21**(4): 1365-1370.

Trioctylphosphine oxide capped cadmium selenide quantum dots, synthesized in organic media were rendered water soluble by silica overcoating. Silanisation was done by a simple reverse microemulsion method using aminopropyl silane as the silica precursor. Further, the strong photoluminescence of the silica-coated CdSe quantum dots has been utilized to visualize rabbit adipose tissue-derived mesenchymal stem cells (RADMSCs) and Daltons lymphoma ascites (DLA) cancerous cells in vitro. Subsequently the in vivo fluorescence behaviours of QDs in the tissues were also demonstrated by intravenous administration of the QDs in Swiss albino mice. The fluorescence microscopic images in the stem cells, cancer cells and semi-thin sections of mice organs proved the strong luminescence property of silica-coated quantum dots under biological systems. These results establish silica-coated CdSe QDs as extremely useful tools for molecular imaging and cell tracking to study the cell division and metastasis of cancer and other diseases.

Vinduska, V., et al. (2021). "Exosomal Surface Protein Detection with Quantum Dots and Immunomagnetic Capture for Cancer Detection." Nanomaterials (Basel) **11**(7).

Exosomes carry molecular contents reflective of parental cells and thereby hold great potential as a source of biomarkers for non-invasive cancer detection and monitoring. However, simple and rapid exosomal molecular detection remains challenging. Here, we report a facile method for exosome surface protein detection using quantum dot coupled with immunomagnetic capture and enrichment. In this method, exosomes were captured by magnetic beads based on CD81 protein expression. Surface protein markers of interest were recognized by primary antibody and then detected by secondary antibody-conjugated quantum dot with fluorescent spectroscopy. Validated by ELISA, our method can specifically detect different surface markers on exosomes from different cancer cell lines and differentiate cancer exosomes from normal exosomes. The clinical potential was demonstrated with pilot plasma samples using HER2-positive breast cancer as the disease model. The results show that exosomes from HER2-positive breast cancer patients exhibited a five times higher level of HER2 expression than healthy controls. Exosomal HER2 showed strong diagnostic power for HER2-positive patients, with the area under the curve of 0.969. This quantum dot-based exosome method is rapid (less than 5 h) and only requires microliters of diluted plasma without pre-purification, practical for routine use for basic vesicle research, and clinical applications.

Vinnarasi, S., et al. (2020). "Structural insights into the anti-cancer activity of quercetin on G-tetrad, mixed G-tetrad, and G-quadruplex DNA using quantum chemical and molecular dynamics simulations." J Biomol Struct Dyn **38**(2): 317-339.

Human telomerase referred as 'terminal transferase' is a nucleoprotein enzyme which inhibits the disintegration of telomere length and act as a drug target for the anticancer therapy. The tandem repeating structure of telomere sequence forms the guanine-rich quadruplex structures that stabilize stacked tetrads. In our present work, we have investigated the interaction of quercetin with DNA tetrads using DFT. Geometrical analysis revealed that the influence of quercetin drug induces the structural changes into the DNA tetrads. Among DNA tetrads, the quercetin stacked with GCGC tetrad has the highest interaction energy of -88.08 kcal/mol. The binding mode and the structural stability are verified by the absorption spectroscopy method. The longer wavelength was found at 380 nm and it exhibits bathochromic shift. The findings help us to understand the binding nature of quercetin drug with DNA tetrads and it also inhibits the telomerase activity. Further, the quercetin drug interacted with G-quadruplex DNA by using molecular dynamics (MD) simulation studies for 100 ns simulation at different temperatures and different pH levels (T = 298 K, 320 K and pH = 7.4, 5.4). The structural stability of the quercetin with G-quadruplex structure is confirmed by RMSD. For the acidic condition (pH = 5.4), the binding affinity is higher toward G-quadruplex DNA, this result resembles that the quercetin drug is well interacted with G-quadruplex DNA at acidic condition (pH = 7.4) than the neutral

condition. The obtained results show that quercetin drug stabilizes the G-quadruplex DNA, which regulates telomerase enzyme and it potentially acts as a novel anti-cancer agent.Communicated by Ramaswamy H. Sarma.

Vyshnava, S. S., et al. (2022). "Quantum dots based in-vitro co-culture cancer model for identification of rare cancer cell heterogeneity." Sci Rep **12**(1): 5868.

Cancer cell heterogeneity (CCH) is crucial in understanding cancer progression and metastasis. The CCH is one of the stumbling blocks in modern medicine's therapeutics and diagnostics . An in-vitro model of co-culture systems of MCF-7, HeLa, HEK-293, with THP-1 cells showed the occurrence of EpCAM positive (EpCAM+) and EpCAM negative (EpCAM-) heterogenetic cancer cell types labeled with the Quantum Dot antibody conjugates (QD(Ab)). This in-vitro model study could provide insights into the role of rare cancer cells manifestation and their heterogeneity in metastatic progression and risk for severe infections in these patients. We successfully report the presence of CCH based on the fluorescence ratios of the co-cultured cancer cells when treated with the QD(Ab). These short-term mimic co-cultures give a compelling and quite associated model for assessing early treatment responses in various cancers.

Wagner, M. K., et al. (2010). "Use of quantum dots in the development of assays for cancer biomarkers." Anal Bioanal Chem **397**(8): 3213-3224.

Biomarker assays may be useful for screening and diagnosis of cancer if a set of molecular markers can be quantified and statistically differentiated between cancerous cells and healthy cells. Markers of disease are often present at very low concentrations, so methods capable of low detection limits are required. Quantum dots (QDs) are nanoparticles that are emerging as promising probes for ultrasensitive detection of cancer biomarkers. QDs attached to antibodies, aptamers, oligonucleotides, or peptides can be used to target cancer markers. Their fluorescent properties have enabled QDs to be used as labels for in-vitro assays to quantify biomarkers, and they have been investigated as in-vivo imaging agents. QDs can be used as donors in assays involving fluorescence resonance energy transfer (FRET), or as acceptors in bioluminescence resonance energy transfer (BRET). The nanoparticles are also capable of electrochemical detection and are potentially useful for "lab-on-a-chip" applications. Recent developments in silicon QDs, non-blinking QDs, and QDs with reduced-size and controlled-valence further make these QDs bioanalytically attractive because of their low toxicity, biocompatibility, high quantum yields, and diverse surface modification flexibility. The potential of multiplexed sensing using QDs with different wavelengths of emission is promising for simultaneous detection of multiple biomarkers of disease.

Wahab, R., et al. (2012). "Platinum quantum dots and their cytotoxic effect towards myoblast cancer cells (C2C12)." J Biomed Nanotechnol **8**(3): 424-431.

The cytotoxic effect towards myoblast cancer cells (C3C12) of well-crystalline colloidal Pt quantum dots (QDs) was examined and presented in this paper. The Pt QDs were synthesized by facile colloidal process and characterized by transmission electron microscopy (TEM) and high-resolution TEM (HR-TEM), which confirmed that the QDs are prepared in high-density, possessing a well-crystalline structure. To examine the cytotoxicity, various doses of as-prepared QDs were treated with C2C12 myoblast cancer cells at different incubation intervals; 24, 48, 72, and 96 hours, and the viability of cells was analyzed with MTT assay. The detailed analyses revealed that in the presence of Pt-QDs, with increasing the incubation time, the number of cancer cells decreases. Moreover, with increasing concentration of Pt-QDs, the cancer cell death increases, confirming that the concentration of Pt-QDs has a significant role in controlling the number of cancer cells. The present research demonstrated that Pt-QDs can efficiently be used as anticancer agents.

Walker, K. A., et al. (2012). "Quantum dots for multiplexed detection and characterisation of prostate cancer cells using a scanning near-field optical microscope." PLoS One **7**(2): e31592.

In this study scanning near-field optical microscopy (SNOM) has been utilised in conjunction with quantum dot labelling to interrogate the biomolecular composition of cell membranes. The technique overcomes the limits of optical diffraction found in standard fluorescence microscopy and also yields vital topographic information. The technique has been applied to investigate cell-cell adhesion in human epithelial cells. This has been realised through immunofluorescence labelling of the cell-cell adhesion protein E-cadherin. Moreover, a dual labelling protocol has been optimised to facilitate a comparative study of the adhesion mechanisms and the effect of aberrant adhesion protein expression in both healthy and cancerous epithelial cells. This study reports clear differences in the morphology and phenotype of healthy and cancerous cells. In healthy prostate epithelial cells (PNT2), E-cadherin was predominantly located around the cell periphery and within filopodial extensions. The presence of E-cadherin appeared to be enhanced when cell-cell contact was established. In contrast, examination of metastatic prostate adenocarcinoma cells (PC-3) revealed no E-cadherin labelling around the periphery of the cells. This lack of functional E-cadherin in PC-3 cells coincided with a markedly different

morphology and PC-3 cells were not found to form close cell-cell associations with their neighbours. We have demonstrated that with a fully optimised sample preparation methodology, multiplexed quantum dot labelling in conjunction with SNOM imaging can be successfully applied to interrogate biomolecular localisation within delicate cellular membranes.

Wang, C., et al. (2013). "Enhancing cell nucleus accumulation and DNA cleavage activity of anti-cancer drug via graphene quantum dots." Sci Rep **3**: 2852.

Graphene quantum dots (GQDs) maintain the intrinsic layered structural motif of graphene but with smaller lateral size and abundant periphery carboxylic groups, and are more compatible with biological system, thus are promising nanomaterials for therapeutic applications. Here we show that GQDs have a superb ability in drug delivery and anti-cancer activity boost without any pre-modification due to their unique structural properties. They could efficiently deliver doxorubicin (DOX) to the nucleus through DOX/GQD conjugates, because the conjugates assume different cellular and nuclear internalization pathways comparing to free DOX. Also, the conjugates could enhance DNA cleavage activity of DOX markedly. This enhancement combining with efficient nuclear delivery improved cytotoxicity of DOX dramatically. Furthermore, the DOX/GQD conjugates could also increase the nuclear uptake and cytotoxicity of DOX to drug-resistant cancer cells indicating that the conjugates may be capable to increase chemotherapy efficacy of anti-cancer drugs that are suboptimal due to the drug resistance.

Wang, C., et al. (2021). "Ultrasensitive, high-throughput and multiple cancer biomarkers simultaneous detection in serum based on graphene oxide quantum dots integrated microfluidic biosensing platform." Anal Chim Acta **1178**: 338791.

Biomarkers play an important role in disease diagnosis and prognosis, which demand reliable, sensitive, rapid, and economic detection platform to conduct simultaneous multiple-biomarkers analysis in serum or body liquid. Here, we developed a universal biosensing platform through integrating the advantages of unique nanostructure and biochemistry properties of graphene oxide quantum dots and high throughput and low cost of microfluidic chip for reliable and simultaneous detection of multiple cancer antigen and antibody biomarkers. The performance of the proposed biosensing platform is validated through the representative cancer biomarkers including carcino-embryonic antigen (CEA), carbohydrate antigen 125 (CA125), alpha-fetoprotein (AFP), carbohydrate antigen 199 (CA199) and carbohydrate antigen 153 (CA153). It has a large linear quantification detection regime of 5-6 orders of magnitude and an ultralow detection limit of 1 pg/mL or 0.01 U/mL. Moreover, the proposed biosensing chip is capable of conducting 5-20 kinds of biomarkers from at least 60 persons simultaneously in 40 min with only 2 muL serum of each patient, which essentially reduces the detection cost and time to at least 1/60 of current popular methods. Clinical breast cancer and healthy samples detection results indicated its promising perspective in practical applications including cancer early diagnosis, prognosis, and disease pathogenesis study.

Wang, H., et al. (2015). "Apoptosis and necrosis induced by novel realgar quantum dots in human endometrial cancer cells via endoplasmic reticulum stress signaling pathway." Int J Nanomedicine **10**: 5505-5512.

Realgar (AS4S4) has been used in traditional medicines for malignancy, but the poor water solubility is still a major hindrance to its clinical use. Realgar quantum dots (RQDs) were therefore synthesized with improved water solubility and bioavailability. Human endometrial cancer JEC cells were exposed to various concentrations of RQDs to evaluate their anticancer effects and to explore mechanisms by the MTT assay, transmission electron microscopy (TEM), flow cytometry, real-time reverse transcriptase polymerase chain reaction (RT-PCR) and Western blot analysis. Results revealed that the highest photoluminescence quantum yield of the prepared RQDs was up to approximately 70%, with the average size of 5.48 nm. RQDs induced antipro-liferative activity against JEC cells in a concentration-dependent manner. In light microscopy and TEM examinations, RQDs induced vacuolization and endoplasmic reticulum (ER) dilation in JEC cells in a concentration-dependent manner. ER stress by RQDs were further confirmed by increased expression of GADD153 and GRP78 at both mRNA and protein levels. ER stress further led to JEC cell apoptosis and necrosis, as evidenced by flow cytometry and mitochondrial membrane potential detection. Our findings demonstrated that the newly synthesized RQDs were effective against human endometrial cancer cells. The underlying mechanism appears to be, at least partly, due to ER stress leading to apoptotic cell death and necrosis.

Wang, J., et al. (2021). "Cancer photothermal therapy based on near infrared fluorescent CdSeTe/ZnS quantum dots." Anal Methods **13**(45): 5509-5515.

Micro targeted therapy for cancer has become a hot topic in recent years because of its advantages of little damage to the human body and early treatment of cancer. Therefore, accurate, rapid treatment methods and biofriendly exogenous substances are extremely important. CdTeSe/ZnS core-shell quantum dots (QDs) have great potential in biomedical imaging and biological ablation therapy due to their advantages of

near-infrared radiation, aqueous synthesis and bio-friendliness. In this paper, CdTeSe/ZnS core-shell QDs were prepared by aqueous synthesis, and have near infrared output and excellent photothermal properties. A blue laser was used as the irradiation source and QD fluorescence imaging can accurately calibrate the treatment area. Under the photothermal and photodynamic effects of QDs, apoptosis of hepatoma cells Huh7 was induced, which provides a new micro-nano technology and biofriendly exogenous substances for cancer treatment.

Wang, L., et al. (2018). "Quantum dot-based immunofluorescent imaging and quantitative detection of DNER and prognostic value in prostate cancer." Cancer Biomark **22**(4): 683-691.

DNER, Delta/Notch-like epidermal growth factor (EGF)-related receptor, is a neuron-specific transmembrane protein carrying extracellular EGF-like repeats. The prognostic value of DNER in prostate cancer has not been evaluated. Here we showed that the up-regulation of DNER protein was observed in prostate cancer detected by immunohistochemistry (IHC) and quantum dot-based immunofluorescent imaging and quantitative analytical system (QD-IIQAS). However, a higher accuracy of measurements of DNER expression in prostate cancer was found by QD-IIQAS than by IHC (AUC = 0.817 and 0.617, respectively). DNER was significantly higher in patients undergoing bone metastasis (P = 0.045, RR = 3.624). In addition, DNER overexpression was associated with poor overall survival (OS) (P = 0.028, adjusted HR = 8.564) and recurrence-free survival (RFS) (P = 0.042, adjusted HR = 3.474) in patients suffering prostate cancer. Thus, QD-IIQAS is an easy and accurate method for assessing DNER and the DNER expression was an independent prognostic factor in prostate cancer.

Wang, L. and J. Yan (2019). "Superficial synthesis of photoactive copper sulfide quantum dots loaded nano-graphene oxide sheets combined with near infrared (NIR) laser for enhanced photothermal therapy on breast cancer in nursing care management." J Photochem Photobiol B **192**: 68-73.

The purpose of this report was to progress the advancement of nanotechnology combined with near-infrared (NIR) laser-mediated treatment for enhancing efficiency against breast cancer (MCF-7) cells. The physic-chemical interactions and properties of the surface improved nano-Graphene oxide (nGO) sheets with Copper Sulfide (CuS) quantum dots were analyzed by selected exclusive analytical methods. The cytotoxicity effect of nGO was investigated by various in vitro assays. The surface activated nGO was exhibited its maximum absorption peak at 233 nm. The XRD analysis shows that the intensity of graphite was decreased and new peak arises around 2=11.4o with an interlayer distance of 0.728 to 0.828 nm. In addition, microscopic studies demonstrated that the synthesized nGO was found as a transparent layer with the crispy structure as well as few layers appear as nanoflakes. The cell toxicity enhancement on MCF-7 breast cancer cells was highly influenced by the concentration of CuSQDs loaded nGO sheets with an assessed IC50 value was 100 mug/mL. The fluorescence microscopic visualization was confirmed the cells apoptotic morphological variations and cell death in CuSQDs-nGO treated breast cancer (MCF-7) cell line. Furthermore, the augmented level of Caspase-3, ROS and LDH activities of cancer cells were exhibited after CuSQDs-nGO treatment. Therefore, the present detailed biological investigations demonstrated that NIR-combined with surface activated CuSQDs-nGO presented a significant enhancement of cytotoxic effect against MCF-7 breast cancer cell lines by photothermal therapy (PTT).

Wang, L. W., et al. (2015). "Quantum dots-based tissue and in vivo imaging in breast cancer researches: current status and future perspectives." Breast Cancer Res Treat **151**(1): 7-17.

As the most common malignant tumor for females, breast cancer (BC) is a highly heterogeneous disease regarding biological behaviors. Precisely targeted imaging on BC masses and biomarkers is critical to BC detection, treatment, monitoring, and prognostic evaluation. As an important imaging technique, quantum dots (QDs)-based imaging has emerged as a promising tool in BC researches owe to its outstanding optical properties. However, few reviews have been specifically devoted to discussing applications of QDs-based imaging in BC researches. This review summarized recent promising works in QDs-based tissue and in vivo imaging for BC studies. Physicochemical and optical properties of QDs and its potential applications were briefly described first. Then QDs-based imaging studies in BC were systematically reviewed, including tissue imaging for studying biomarkers interactions, and evaluating prognostic biomarkers, in vivo imaging for mapping axillary lymphatic system, showing BC xenograft tumor, and detecting BC metastases. At last, the future perspectives with special emphasis on the potential clinical applications have also been discussed. Potential applications of QDs-based imaging on clinical BC in the future are mainly focused on tissue study, especially in BC molecular pathology due to its optimal optical properties and quantitative information capabilities on multiple biomarkers.

Wang, L. W., et al. (2016). "Quantum dots-based double imaging combined with organic dye imaging to establish

an automatic computerized method for cancer Ki67 measurement." Sci Rep **6**: 20564.

As a widely used proliferative marker, Ki67 has important impacts on cancer prognosis, especially for breast cancer (BC). However, variations in analytical practice make it difficult for pathologists to manually measure Ki67 index. This study is to establish quantum dots (QDs)-based double imaging of nuclear Ki67 as red signal by QDs-655, cytoplasmic cytokeratin (CK) as yellow signal by QDs-585, and organic dye imaging of cell nucleus as blue signal by 4',6-diamidino-2-phenylindole (DAPI), and to develop a computer-aided automatic method for Ki67 index measurement. The newly developed automatic computerized Ki67 measurement could efficiently recognize and count Ki67-positive cancer cell nuclei with red signals and cancer cell nuclei with blue signals within cancer cell cytoplasmic with yellow signals. Comparisons of computerized Ki67 index, visual Ki67 index, and marked Ki67 index for 30 patients of 90 images with Ki67 </= 10% (low grade), 10% < Ki67 < 50% (moderate grade), and Ki67 >/= 50% (high grade) showed computerized Ki67 counting is better than visual Ki67 counting, especially for Ki67 low and moderate grades. Based on QDs-based double imaging and organic dye imaging on BC tissues, this study successfully developed an automatic computerized Ki67 counting method to measure Ki67 index.

Wang, M., et al. (2021). "Fluorescence imaging-guided cancer photothermal therapy using polydopamine and graphene quantum dot-capped Prussian blue nanocubes." RSC Adv **11**(15): 8420-8429.

In recent years, imaging-guided photothermal tumor ablation has attracted intense research interest as one of the most exciting strategies for cancer treatment. Herein, we prepared polydopamine and graphene quantum dot-capped Prussian blue nanocubes (PB@PDA@GQDs, PBPGs) with high photothermal conversion efficiency and excellent fluorescence performance for imaging-guided cancer treatment. Transmission electron microscopy (TEM), UV-vis absorption spectroscopy (UV-vis), fluorescence spectroscopy, and X-ray photoelectron spectroscopy (XPS) were employed to characterize their morphology and structures. The photothermal conversion efficiency and therapeutic effect were evaluated in vitro and in vivo. Results revealed that this nanoagent had excellent biocompatibility and enhanced the photothermal effect compared to blue nanocubes (PBs) and polydopamine-capped Prussian blue nanocubes (PB@PDA, PBPs). Therefore, our study may open a new path for the production of PB-based nanocomposites as theranostic nanoagents for imaging-guided photothermal cancer treatment.

Wang, M., et al. (2018). "Ultrasmall black phosphorus quantum dots: synthesis, characterization, and application in cancer treatment." Analyst **143**(23): 5822-5833.

Black phosphorus quantum dots (BPQDs) are gaining popularity for applications in various fields because of their unique advantages. For biomedical applications, good biosafety is a prerequisite for the use of BPQDs in vivo. However, currently, little information is available about their basic properties and biocompatibility, which are of great importance for potential biomedical applications. In this work, we prepared BPQDs by an improved solvothermal method and evaluated their fluorescence, biocompatibility, and photothermal therapy (PTT) effectiveness. First, the structures and functions of the BPQDs were investigated at the cellular and molecular levels. It was found that the fluorescence of the BPQDs is wavelength-dependent and that they absorb in the UV-vis range; also, their quantum yield reached 10.2%. In particular, we considered the morphology and lysis of human red blood cells, in vivo blood coagulation, and plasma recalcification profiles. We found that the BPQDs have excellent biocompatibility and hemocompatibility with blood components. Overall, concentrations of the BPQDs </=0.5 mg mL-1 had few adverse effects on blood components. The resulting BPQDs can efficiently convert near-infrared (NIR) light into heat; thus, they are suitable as a novel nanotheranostic agent for PTT of cancer. Meanwhile, the results of serum biochemistry tests revealed that the indicators were at similar levels for mice exposed to BPQDs and for control mice. Furthermore, from biodistribution analysis of the BPQDs, no apparent pathological damage was observed in any organs, especially in the spleen and kidneys, during the 30 day period. Our research indicates that the BPQDs have bio-imaging capability and biocompatibility and highlights their great potential in the therapy of cancer.

Wang, S., et al. (2016). "Quantitative detection of the tumor-associated antigen large external antigen in colorectal cancer tissues and cells using quantum dot probe." Int J Nanomedicine **11**: 235-247.

The large external antigen (LEA) is a cell surface glycoprotein that has been proven to be highly expressed in colorectal cancer (CRC) as a tumor-associated antigen. To evaluate and validate the relationship between LEA expression and clinical characteristics of CRC with high efficiency, LEA expression levels were detected in 85 tissue blocks from CRC patients by quantum dot-based immunohistochemistry (QD-IHC) combined with imaging quantitative analysis using quantum dots with a 605 nm emission wavelength (QD605) conjugated to an ND-1 monoclonal antibody against LEA as a probe.

Conventional IHC was performed in parallel for comparison. Both QD-IHC and conventional IHC showed that LEA was specifically expressed in CRC, but not in non-CRC tissues, and high LEA expression was significantly associated with a more advanced T-stage ($P<0.05$), indicating that LEA is likely to serve as a CRC prognostic marker. Compared with conventional IHC, receiver operating characteristic analysis revealed that QD-IHC possessed higher sensitivity, resulting in an increased positive detection rate of CRC, from 70.1% to 89.6%. In addition, a simpler operation, objective analysis of results, and excellent repeatability make QD-IHC an attractive alternative to conventional IHC in clinical practice. Furthermore, to explore whether the QD probes can be utilized to quantitatively detect living cells or single cells, quantum dot-based immunocytochemistry (QD-ICC) combined with imaging quantitative analysis was developed to evaluate LEA expression in several CRC cell lines. It was demonstrated that QD-ICC could also predict the correlation between LEA expression and the T-stage characteristics of the cell lines, which was confirmed by flow cytometry. The results of this study indicate that QD-ICC has the potential to noninvasively detect rare circulating tumor cells in clinical samples in real clinical applications.

Wang, X., et al. (2020). "Ultrasmall BiOI Quantum Dots with Efficient Renal Clearance for Enhanced Radiotherapy of Cancer." Adv Sci (Weinh) **7**(6): 1902561.

Emerging strategies involving nanomaterials with high-atomic-number elements have been widely developed for radiotherapy in recent years. However, the concern regarding their potential toxicity caused by long-term body retention still limits their further application. In this regard, rapidly clearable radiosensitizers are highly desired for practical cancer treatment. Thus, in this work, ultrasmall BiOI quantum dots (QDs) with efficient renal clearance characteristic and strong permeability inside solid tumor are designed to address this issue. Additionally, considering that injection methods have great influence on the biodistribution and radiotherapeutic efficacy of radiosensitizers, two common injection methods including intratumoral injection and intravenous injection are evaluated. The results exhibit that intratumoral injection can maximize the accumulation of radiosensitizers within a tumor compared to intravenous injection and further enhance radiotherapeutic efficacy. Furthermore, the radiosensitizing effect of BiOI QDs is revealed, which is not only attributed to the radiation enhancement of high-Z elements but also is owed to the *OH production via catalyzing overexpressed H2O2 within a tumor by BiOI QDs under X-ray irradiation. As a result, this work proposes a treatment paradigm to employ ultrasmall radiosensitizers integrated with local intratumoral injection to realize rapid clearance and high-efficiency radiosensitization for cancer therapy.

Wang, Y., et al. (2017). "The Evaluation of Colorectal Cancer Risk in Serum by anti-DESMIN-conjugated CdTe/CdS Quantum Dots." Clin Lab **63**(3): 579-586.

BACKGROUND: DESMIN is a novel prognostic predictor and therapeutic target for colorectal cancer (CRC). Enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence (ELC) assays are large-scale and highcost projects; therefore, it is necessary to develop a new, fast, and simple yet highly sensitive and specific method to detect DESMIN in serum. Semiconducting quantum dots (QDs) possess high fluorescence quantum yield, stability against photobleaching, and size-controlled luminescence properties, thus being utilized in photoelectrochemical tumor marker detection, especially in ameliorating the diagnostic value in complex biological ambient ionization. However, CdTe/CdS quantum dots (QDs) have not been applied in detecting DESMIN in serum. METHODS: DESMIN in serum has been established using anti-DESMIN-conjugated CdTe/CdS quantum dots (QDs) and measurements. The assay sensitivity was determined by measurement of quenched fluorescence intensity of DESMIN at 0.1, 0.5, 1.0, 2.0, or 5.0 ng/mL in PBS or 0.25%, 0.5%, 1.0%, 2.0%, or 5% human serum diluted in PBS. The assay was optimized under different pH (7.00 - 7.40) for different reaction durations (10 - 60 minutes). The specificity of anti-DESMIN-QDs was determined by testing the interference of DESMIN activity with CEA, IgG, or AFP, each at 1 ng/mL. RESULTS: Under the optimized incubation time (30 minutes) at room temperature and optimal pH 7.1 - 7.2, a correlation between the decreased fluorescence intensity of anti-DESMIN-conjugated CdTe/CdS QDs and the concentration of DESMIN in the range from 0.05 to 100 ng/mL, was established. The sensitivity for the detection of DESMIN in the range from 0.05 to 100 ng/mL, with a detection limit of 0.02 ng/mL. The assay presented a high specificity because the anti-DESMIN-conjugated CdTe/CdS QDs only reacted with ABR1B10 in the sera in the presence of CEA, IgG or AFP. CONCLUSIONS: The immunofluorescence assay to detect DESMIN in serum using anti-DEMSIN-conjugated CdTe/ CdS QDs was fast and simple yet presented high sensitivity and specificity. Our method provides a promising tool for early prediction of CRC risk.

Wang, Y., et al. (2017). "Quantum-Dot-Based Theranostic Micelles Conjugated with an Anti-EGFR Nanobody for Triple-Negative Breast Cancer Therapy." ACS Appl Mater Interfaces **9**(36): 30297-30305.

A quantum-dot (QD)-based micelle conjugated with an anti-epidermal growth factor receptor (EGFR) nanobody (Nb) and loaded with an anticancer drug, aminoflavone (AF), has been engineered for EGFR-overexpressing cancer theranostics. The near-infrared (NIR) fluorescence of the indium phosphate core/zinc sulfide shell QDs (InP/ZnS QDs) allowed for in vivo nanoparticle biodistribution studies. The anti-EGFR nanobody 7D12 conjugation improved the cellular uptake and cytotoxicity of the QD-based micelles in EGFR-overexpressing MDA-MB-468 triple-negative breast cancer (TNBC) cells. In comparison with the AF-encapsulated nontargeted (i.e., without Nb conjugation) micelles, the AF-encapsulated Nb-conjugated (i.e., targeted) micelles accumulated in tumors at higher concentrations, leading to more effective tumor regression in an orthotopic triple-negative breast cancer xenograft mouse model. Furthermore, there was no systemic toxicity observed with the treatments. Thus, this QD-based Nb-conjugated micelle may serve as an effective theranostic nanoplatform for EGFR-overexpressing cancers such as TNBCs.

Wang, Z. Y., et al. (2021). "A copper-free and enzyme-free click chemistry-mediated single quantum dot nanosensor for accurate detection of microRNAs in cancer cells and tissues." Chem Sci **12**(31): 10426-10435.

MicroRNAs (miRNAs) play key roles in the post-transcriptional regulation of genes, and their aberrant expression may disturb the normal gene regulation network to induce various diseases, and thus accurate detection of miRNAs is essential to early clinical diagnosis. Herein, we develop for the first time a single-quantum dot (QD)-based Forster resonance energy transfer (FRET) nanosensor to accurately detect miRNAs based on copper-free and enzyme-free cycling click chemistry-mediated tricyclic ligase chain reaction (LCR) amplification. We design four DNA probes namely DNA probes 1-4, with DNA probes 1 and 3 being modified with azide (N3) and DNA probes 2 and 4 being modified with dibenzocyclooctyne (DBCO). When target miRNA is present, DNA probes 1 and 2 can proceed via copper-free and enzyme-free click chemistry to generate the probes 1-2 ligation product. Subsequently, DNA probes 3 and 4 can hybridize with the probes 1-2 ligation product to generate the probes 3-4 ligation product. Both the probes 1-2 ligation product and probes 3-4 ligation product can act as the templates to initiate cycling click chemistry-mediated tricyclic LCR amplification whose products can be easily measured by the single-QD-based FRET nanosensor. This assay does not involve any enzymatic reverse transcription, copper catalyst, and ligase enzyme, and it exhibits excellent selectivity, high sensitivity, and the capability of differentiating even single-base mismatches. Moreover, this nanosensor can accurately quantify miRNA-155 even at the single-cell level, and it can distinguish the miRNA-155 expression in tissues of healthy persons and nonsmall cell lung cancer (NSCLC) patients.

Wang, Z. Y., et al. (2022). "Hydroxymethylation-Specific Ligation-Mediated Single Quantum Dot-Based Nanosensors for Sensitive Detection of 5-Hydroxymethylcytosine in Cancer Cells." Anal Chem **94**(27): 9785-9792.

5-Hydroxymethylcytosine (5hmC) modification is a key epigenetic regulator of cellular processes in mammalian cells, and its misregulation may lead to various diseases. Herein, we develop a hydroxymethylation-specific ligation-mediated single quantum dot (QD)-based fluorescence resonance energy transfer (FRET) nanosensor for sensitive quantification of 5hmC modification in cancer cells. We design a Cy5-modified signal probe and a biotinylated capture probe for the recognition of specific 5hmC-containing genes. 5hmC in target DNA can be selectively converted by T4 beta-glucosyltransferase to produce a glycosyl-modified 5hmC, which cannot be cleaved by methylation-insensitive restriction enzyme MspI. The glycosylated 5hmC DNA may act as a template to ligate a signal probe and a capture probe, initiating hydroxymethylation-specific ligation to generate large amounts of biotin-/Cy5-modified single-stranded DNAs (ssDNAs). The assembly of biotin-/Cy5-modified ssDNAs onto a single QD through streptavidin-biotin interaction results in FRET and consequently the generation of a Cy5 signal. The nanosensor is very simple without the need for bisulfite treatment, radioactive reagents, and 5hmC-specific antibodies. Owing to excellent specificity and high amplification efficiency of hydroxymethylation-specific ligation and near-zero background of a single QD-based FRET, this nanosensor can quantify 5hmC DNA with a limit of detection of 33.61 aM and a wider linear range of 7 orders of magnitude, and it may discriminate the single-nucleotide difference among 5hmC, 5-methylcytosine, and unmodified cytosine. Moreover, this nanosensor can distinguish as low as a 0.001% 5hmC DNA in complex mixtures, and it can monitor the cellular 5hmC level and discriminate cancer cells from normal cells, holding great potential in biomedical research and clinical diagnostics.

Waniczek, D., et al. (2018). "Assessment of PI3K/AKT/PTEN signaling pathway activity in colorectal cancer using quantum dot-conjugated antibodies." Oncol Lett **15**(1): 1236-1240.

In certain patients with advanced colorectal cancer, loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) activity is observed. PTEN

is a major gatekeeper gene of the AKT serine/threonine kinase (AKT) signaling pathway responsible for the proliferative activity of cells. The assessment of AKT activity may be a prognostic factor or a predictor of response to the targeted therapies against particular signaling proteins. To precisely identify the cause and the place of the pathway deregulation, it is necessary to identify phosphorylation states and concentrations of several proteins located at different levels of the regulatory cascade. In the present study, we propose the simultaneous use of specific antibodies conjugated with different quantum dots to highlight the nature of AKT/PKB cascade deregulation in patients with colorectal cancer and the loss of PTEN expression in tumor tissue. Fifty patients with colorectal cancer of no specific location were enrolled in the study. The expression of the PTEN protein, and concentrations of phosphorylated/activated forms of 3-Phosphoinositide-dependent kinase 1 (PDK1) and AKT were assessed using quantum dot-conjugated antibodies. In patients with a diminished or complete loss of the PTEN expression in the tumor tissue increased levels of activated/phosphorylated forms of PDK1 (Phospho-PDK1-Ser241) and AKT (Phospho-AKT-Thr308) proteins were found, which are responsible for the permanent activation of the phosphoinositide 3-kinase/AKT/PTEN signaling pathway in certain cases of colorectal cancer.

Wei, W., et al. (2014). "DNA-templated assembly of a heterobivalent quantum dot nanoprobe for extra- and intracellular dual-targeting and imaging of live cancer cells." Angew Chem Int Ed Engl **53**(22): 5573-5577.

Quantum dots (QDs) hold great promise for the molecular imaging of cancer because of their superior optical properties. Although cell-surface biomarkers can be readily imaged with QDs, non-invasive live-cell imaging of critical intracellular cancer markers with QDs is a great challenge because of the difficulties in the automatic delivery of QD probes to the cytosol and the ambiguity of intracellular targeting signals. Herein, we report a new type of DNA-templated heterobivalent QD nanoprobes with the ability to target and image two spatially isolated cancer markers (nucleolin and mRNA) present on the cell surface and in the cell cytosol. Bypassing endolysosomal sequestration, this type of QD nanoprobes undergo macropinocytosis following the nucleolin targeting and then translocate to the cytosol for mRNA targeting. Fluorescence resonance energy transfer (FRET) based confocal microscopy enables unambiguous signal deconvolution of mRNA-targeted QD nanoprobes inside cancer cells.

Wen, C. Y., et al. (2016). "Fluorescent/magnetic micro/nano-spheres based on quantum dots and/or magnetic nanoparticles: preparation, properties, and their applications in cancer studies." Nanoscale **8**(25): 12406-12429.

The study of cancer is of great significance to human survival and development, due to the fact that cancer has become one of the greatest threats to human health. In recent years, the rapid progress of nanoscience and nanotechnology has brought new and bright opportunities to this field. In particular, the applications of quantum dots (QDs) and magnetic nanoparticles (MNPs) have greatly promoted early diagnosis and effective therapy of cancer. In this review, we focus on fluorescent/magnetic micro/nano-spheres based on QDs and/or MNPs (we may call them "nanoparticle-sphere (NP-sphere) composites") from their preparation to their bio-application in cancer research. Firstly, we outline and compare the main four kinds of methods for fabricating NP-sphere composites, including their design principles, operation processes, and characteristics (merits and limitations). The NP-sphere composites successfully inherit the unique fluorescence or magnetic properties of QDs or MNPs. Moreover, compared with the nanoparticles (NPs) alone, the NP-sphere composites show superior properties, which are also discussed in this review. Then, we summarize their recent applications in cancer research from three aspects, that is: separation and enrichment of target tumor cells or biomarkers; cancer diagnosis mainly through medical imaging or tumor biomarker detection; and cancer therapy via targeted drug delivery systems. Finally, we provide some perspectives on the future challenges and development trends of the NP-sphere composites.

Wo, F., et al. (2016). "A Multimodal System with Synergistic Effects of Magneto-Mechanical, Photothermal, Photodynamic and Chemo Therapies of Cancer in Graphene-Quantum Dot-Coated Hollow Magnetic Nanospheres." Theranostics **6**(4): 485-500.

In this study, a multimodal therapeutic system was shown to be much more lethal in cancer cell killing compared to a single means of nano therapy, be it photothermal or photodynamic. Hollow magnetic nanospheres (HMNSs) were designed and synthesized for the synergistic effects of both magneto-mechanical and photothermal cancer therapy. By these combined stimuli, the cancer cells were structurally and physically destroyed with the morphological characteristics distinctively different from those by other therapeutics. HMNSs were also coated with the silica shells and conjugated with carboxylated graphene quantum dots (GQDs) as a core-shell composite: HMNS/SiO2/GQDs. The composite was further loaded with an anticancer drug doxorubicin (DOX) and stabilized with liposomes. The multimodal system was able to kill cancer cells with four different therapeutic mechanisms in a synergetic and multilateral fashion, namely, the magnetic field-

mediated mechanical stimulation, photothermal damage, photodynamic toxicity, and chemotherapy. The unique nanocomposites with combined mechanical, chemo, and physical effects will provide an alternative strategy for highly improved cancer therapy efficiency.

Wu, B., et al. (2021). "Trifunctional Graphene Quantum Dot@LDH Integrated Nanoprobes for Visualization Therapy of Gastric Cancer." Adv Healthc Mater **10**(16): e2100512.

Visualization technology has become a trend in tumor therapy in recent years. The superior optical properties of graphene quantum dots (GQDs) make them suitable candidates for tumor diagnosis, but their tumor targeting and drug-carrying capacities are still not ideal for treatment. Sulfur-doped graphene quantum dots (SGQDs) with stable fluorescence are prepared in a previous study. A reliable strategy by associating layered double hydroxides (LDHs) and etoposide (VP16) is designed for precise visualization therapy. Trifunctional LDH@SGQD-VP16 integrated nanoprobes can simultaneously achieve targeted aggregation, fluorescence visualization, and chemotherapy. LDH@SGQD-VP16 can accumulate in the tumor microenvironment, owing to pH-sensitive properties and long-term photostability in vivo, which can provide a basis for cancer targeting, real-time imaging, and effect tracking. The enhanced therapeutic and attenuated side effects of VP16 are demonstrated, and the apoptosis caused by LDH@SGQD-VP16 is approximately 2.7 times higher than that of VP16 alone, in HGC-27 cells. This work provides a theoretical and experimental basis for LDH@SGQD-VP16 as a potential multifunctional agent for visualization therapy of gastric cancer.

Wu, C., et al. (2019). "Highly efficient cascading synergy of cancer photo-immunotherapy enabled by engineered graphene quantum dots/photosensitizer/CpG oligonucleotides hybrid nanotheranostics." Biomaterials **205**: 106-119.

Currently, photoimmunotherapy based on a theranostic nanoplatform emerges as a promising modality in advanced cancer therapy. In this study, a new type of versatile nanoassemblies (denoted as PC@GCpD(Gd)) was rationally designed by integrating the polydopamine stabilized graphene quantum dots (GQD)-photosensitizer nanocomposites (denoted as GCpD), immunostimulatory polycationic polymer/CpG oligodeoxynucleotide (CpG ODN) nanoparticles (denoted as PC) and Gd(3+)/Cy3 imaging probes for dual magnetic resonance/fluorescence imaging-guided photoimmunotherapy. PC@GCpD(Gd) effectively killed the tumor cells through the amplified photothermal and photodynamic effects mediated by GCpD, and contemporaneously delivered CpG ODN to the targeted endosomal Toll-like receptor 9 (TLR9) to continuously stimulate the secretion of proinflammatory cytokines and the maturation of dendritic cells, thereby resulting in the activation and infiltration of T lymphocytes. As a result, PC@GCpD(Gd) achieved robust inhibition efficiency to almost completely suppress the EMT6 murine mammary cancer model under laser irradiation, implying the superior synergy of combined photoimmunotherapy. Moreover, the in vivo delivery and biodistribution of PC@GCpD(Gd) could be tracked using the high-quality bimodal magnetic resonance imaging/fluorescence imaging. This study highlighted the potent prospect of hybrid PC@GCpD(Gd) nanoassemblies for precise cancer photoimmunotherapy with a cascading effect.

Wu, C., et al. (2015). "A recognition-before-labeling strategy for sensitive detection of lung cancer cells with a quantum dot-aptamer complex." Analyst **140**(17): 6100-6107.

A highly specific recognition-before-labeling strategy has been developed for sensitive detection of non-small cell lung cancer A549 cells, by using fluorescent QDs as signal units and DNA aptamers as recognition elements. A QD-aptamer system used for cell imaging and bioanalysis mostly relies on the recognition-after-labeling strategy in which aptamers were firstly labeled with QDs and then the QD-aptamer conjugates as a whole were utilized for specific recognition. Here in our strategy, aptamers were used firstly to recognize target cells, and then fluorescent QDs were sequentially added to bind the aptamers and light the target cells. The proposed recognition-before-labeling strategy didn't require the complex process of QD functionalization, and avoided the possible impact on the aptamer configuration from steric hindrance. Meanwhile, QDs, with strong fluorescence and good photostability, also give this method a high signal-to-background ratio (S/B). The recognition-before-labeling strategy is simple and sensitive, suggesting a new method for in vitro diagnostic assays of cancer cells.

Wu, C., et al. (2010). "Probing the dynamic effect of cys-CdTe quantum dots toward cancer cells in vitro." Chem Res Toxicol **23**(1): 82-88.

The application of quantum dots (QDs) in various biomedical areas requires detailed studies of their toxicity. We report a new strategy for probing the biocompatibility of these nanocrystals, namely, a dynamic investigation of cellular uptake images, cell growth curves, metabolic activity changes, and apoptosis aspects of cadmium telluride QDs capped with cysteamine (Cys-CdTe QDs) on human hepatocellular carcinoma SMMC-7721 cells. We used a real-time cell electronic sensing (RT-CES) system in combination with fluorescence microscopy, 3-(4,5-dimethyl-thiazol-

zyl)-2,5-diphenyltetrazolium bromide assay, and flow cytometry (FCM) analysis. As observed from fluorescence images and RT-CES system results, Cys-CdTe QDs can readily bind on the cell plasma membrane and then enter into the cancer cell, causing decreased adherence of cancer cells during the initial 6-12 h, while the metabolic activity apparently decreased. After 24 h, the metabolic activity of the cancer cells was significantly reduced, with continued reduction in metabolic activity observed at even longer incubation times. Moreover, FCM observation and DNA fragmentation analysis clearly indicate apoptosis-related phenomena when SMMC-7721 cells were treated with the Cys-CdTe QDs. Thus, our study reveals details of the cellular aging and death process induced by Cys-CdTe QDs.

Wu, Q., et al. (2015). "Quantum dots decorated gold nanorod as fluorescent-plasmonic dual-modal contrasts agent for cancer imaging." Biosens Bioelectron **74**: 16-23.

Constructing integrative optical bioprobe with both fluorophores and plasmonic functional groups is of particular interest in precise co-localized bio-imaging probe development. Herein, we fabricated a novel hierarchical complex nanoparticle with fluorescent and plasmonic components spatially separated, which is composed of highly brilliant CdSe/CdS/ZnS QDs decorated gold nanorod (AuNR) with silicon coating. This complex structure served as an efficient dual-modality imaging contrast agent, where the potential fluorescence resonance energy transfer (FRET) between QDs and AuNR was avoided by the intermediate silica layer as well as minimized spectral overlap between QDs and AuNRs. The high-density loading of QDs was achieved by thiol-metal affinity driven assembly of hydrophobic QDs with thiolated AuNR@SiO2 substrate, which is able to show a strong fluorescence emission. After amphiphilic organosilica-mediated phase transferring and functionalization with transferrin (Tf), these nanoparticles entered A549 cells and exhibited high contrasting fluorescent and dark-field signals for co-localized cancer cells imaging. The results demonstrate that these nanoparticles are potential candidates as dual modal probes for fluorescence and dark-field image.

Wu, S., et al. (2016). "Multiplexed detection of lung cancer biomarkers based on quantum dots and microbeads." Talanta **156-157**: 48-54.

We have developed a multiplexed fluoroimmunoassay of three lung cancer biomarkers based on multicolor quantum dots (QDs) as detection elements and micro-magnetic beads as immune carriers. QDs have the ability to simplify multiplexed analysis. In our method, the fluorescent signals derived from three cross-talk-free QD conjugated probes with emission maxima at 525, 585 and 625nm could be analyzed to determine the concentrations of the target proteins. With this system, fragments of cytokeratin 19 (CYRFA 21-1), carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE), were simultaneously detected in a single sample with a low detection limit down to the 1.0ng/mL level (364pg/mL for CYRFA 21-1, 38pg/mL for CEA, 370pg/mL for NSE in a single detection). Additional advantages of the presented method include ease of operation, low cost, and a very low sample volume (20microL).

Wu, X., et al. (2003). "Immunofluorescent labeling of cancer marker Her2 and other cellular targets with semiconductor quantum dots." Nat Biotechnol **21**(1): 41-46.

Semiconductor quantum dots (QDs) are among the most promising emerging fluorescent labels for cellular imaging. However, it is unclear whether QDs, which are nanoparticles rather than small molecules, can specifically and effectively label molecular targets at a subcellular level. Here we have used QDs linked to immunoglobulin G (IgG) and streptavidin to label the breast cancer marker Her2 on the surface of fixed and live cancer cells, to stain actin and microtubule fibers in the cytoplasm, and to detect nuclear antigens inside the nucleus. All labeling signals are specific for the intended targets and are brighter and considerably more photostable than comparable organic dyes. Using QDs with different emission spectra conjugated to IgG and streptavidin, we simultaneously detected two cellular targets with one excitation wavelength. The results indicate that QD-based probes can be very effective in cellular imaging and offer substantial advantages over organic dyes in multiplex target detection.

Xi, J., et al. (2016). "Pd Nanoparticles Decorated N-Doped Graphene Quantum Dots@N-Doped Carbon Hollow Nanospheres with High Electrochemical Sensing Performance in Cancer Detection." ACS Appl Mater Interfaces **8**(34): 22563-22573.

The development of carbon based hollow-structured nanospheres (HNSs) materials has stimulated growing interest due to their controllable structure, high specific surface area, large void space, enhanced mass transport, and good biocompatibility. The incorporation of functional nanomaterials into their core and/or shell opens new horizons in designing functionalized HNSs for a wider spectrum of promising applications. In this work, we report a new type of functionalized HNSs based on Pd nanoparticles (NPs) decorated double shell structured N-doped graphene quantum dots (NGQDs)@N-doped carbon (NC) HNSs, with ultrafine Pd NPs and "nanozyme" NGQDs as dual signal-amplifying nanoprobes, and explore their promising

application as a highly efficient electrocatalyst in electrochemical sensing of a newly emerging biomarker, i.e., hydrogen peroxide (H2O2), for cancer detection. Due to the synergistic effect of the robust and conductive HNS supports and catalytically active Pd NPs and NGQD in facilitating electron transfer, the NGQD@NC@Pd HNS hybrid material exhibits high electrocatalytic activity toward the direct reduction of H2O2 and can promote the electrochemical reduction reaction of H2O2 at a favorable potential of 0 V, which effectively restrains the redox of most electroactive species in physiological samples and eliminates interference signals. The resultant electrochemical H2O2 biosensor based hybrid HNSs materials demonstrates attractive performance, including low detection limit down to nanomole level, short response time within 2 s, as well as high sensitivity, reproducibility, selectivity, and stability, and have been used in real-time tracking of trace amounts of H2O2 secreted from different living cancer cells in a normal state and treated with chemotherapy and radiotherapy.

Xi, M., et al. (2016). "Cancer Feature Selection and Classification Using a Binary Quantum-Behaved Particle Swarm Optimization and Support Vector Machine." Comput Math Methods Med **2016**: 3572705.

This paper focuses on the feature gene selection for cancer classification, which employs an optimization algorithm to select a subset of the genes. We propose a binary quantum-behaved particle swarm optimization (BQPSO) for cancer feature gene selection, coupling support vector machine (SVM) for cancer classification. First, the proposed BQPSO algorithm is described, which is a discretized version of original QPSO for binary 0-1 optimization problems. Then, we present the principle and procedure for cancer feature gene selection and cancer classification based on BQPSO and SVM with leave-one-out cross validation (LOOCV). Finally, the BQPSO coupling SVM (BQPSO/SVM), binary PSO coupling SVM (BPSO/SVM), and genetic algorithm coupling SVM (GA/SVM) are tested for feature gene selection and cancer classification on five microarray data sets, namely, Leukemia, Prostate, Colon, Lung, and Lymphoma. The experimental results show that BQPSO/SVM has significant advantages in accuracy, robustness, and the number of feature genes selected compared with the other two algorithms.

Xiang, Q. M., et al. (2015). "Quantum dot-based multispectral fluorescent imaging to quantitatively study co-expressions of Ki67 and HER2 in breast cancer." Exp Mol Pathol **99**(1): 133-138.

Both Ki67 and HER2 are key prognostic molecules for invasive breast cancer (BC), but the individual relative impacts on prognosis of these molecules are not known. This study was aimed at establishing a quantum dot (QD)-based double-color in-situ quantitative imaging technique to study the co-expressions of Ki67 and HER2, and delineate the individual impacts of these molecules on prognosis. The QD-based fluorescent immunostaining technique could simultaneously image the co-expressions of Ki67 and HER2 in BC specimens, with the former stained as clear red fluorescence in cancer cell nucleus, and the latter as bright green fluorescence on cancer cell membrane. Both Ki67 and HER2 expressions were significantly correlated with 8-year disease free survival (8-DFS) ($P<0.05$). However, the two molecules had different weights in terms of negative impacts on clinical prognosis. The median 8-DFS was statistically significantly shorter in High-Ki67 High-HER2 subgroup than Low-Ki67 High-HER2 subgroup (11.7 vs. 60.1months, $P<0.05$), shorter in High-Ki67 Low-HER2 subgroup than Low-Ki67 Low-HER2 subgroup (16.4 vs. 96.0months, $P<0.01$), shorter in High-Ki67 High-HER2 subgroup than Low-Ki67 Low-HER2 subgroup (11.7 vs. 96.0months, $P<0.01$), but there were no statistically significant differences in median 8-DFS between High-Ki67 Low-HER2 subgroup and High-Ki67 High-HER2 subgroup (11.7 vs. 16.4months, $P=0.586$). The hazard ratio (HR) of Ki67 negative impact on 8-DFS was about 3 fold of that of HER2 (HR 4.493 vs. 1.481). This study demonstrated that QD-based fluorescent imaging technique could help the quantitative study on the co-expressions of Ki67 and HER2 in BC, and Ki67 has a greater negative impact on BC prognosis than HER2.

Xiang, Y., et al. (2010). "Reverse-micelle synthesis of electrochemically encoded quantum dot barcodes: application to electronic coding of a cancer marker." Anal Chem **82**(3): 1138-1141.

Reproducible electrochemically encoded quantum dot (QD) barcodes were prepared using the reverse-micelle synthetic approach. The encoding elements, Zn(2+), Cd(2+), and Pb(2+), were confined within a single QD, which eliminates the cumbersome encapsulation process used by other common nanoparticle-based barcode preparation schemes. The distinct voltammetric stripping patterns of Zn(2+), Cd(2+) and Pb(2+) at distinguishable potentials with controllable current intensities offer excellent encoding capability for the prepared electrochemical (EC) QDs. Additionally, the simultaneous modification of the QD barcode surface with organic ligands during the preparation process make them potentially useful in biomedical research. For proof of concept of their application in bioassays, the EC QD barcodes were further employed as tags for an immunoassay of a cancer marker, carcinoembryonic antigen (CEA). The voltammetric stripping response of the dissolved

bardcode tags was proportional to log[CEA] in the range from 0.01 to 80 ng mL(-1), with a detection limit of 3.3 pg mL(-1). The synthesized EC QD barcodes hold considerable potential in biodetection, encrypted information, and product tracking.

Xie, H., et al. (2020). "Biodegradable Bi2 O2 Se Quantum Dots for Photoacoustic Imaging-Guided Cancer Photothermal Therapy." Small **16**(1): e1905208.

As new 2D layered nanomaterials, Bi2 O2 Se nanoplates have unique semiconducting properties that can benefit biomedical applications. Herein, a facile top-down approach for the synthesis of Bi2 O2 Se quantum dots (QDs) in a solution is described. The Bi2 O2 Se QDs with a size of 3.8 nm and thickness of 1.9 nm exhibit a high photothermal conversion coefficient of 35.7% and good photothermal stability. In vitro and in vivo assessments demonstrate that the Bi2 O2 Se QDs possess excellent photoacoustic (PA) performance and photothermal therapy (PTT) efficiency. After systemic administration, the Bi2 O2 Se QDs accumulate passively in tumors enabling efficient PA imaging of the entire tumors to facilitate imaging-guided PTT without obvious toxicity. Furthermore, the Bi2 O2 Se QDs which exhibit degradability in aqueous media not only have sufficient stability during in vivo circulation to perform the designed therapeutic functions, but also can be discharged harmlessly from the body afterward. The results reveal the great potential of Bi2 O2 Se QDs as a biodegradable multifunctional agent in medical applications.

Xing, Y., et al. (2006). "Molecular profiling of single cancer cells and clinical tissue specimens with semiconductor quantum dots." Int J Nanomedicine **1**(4): 473-481.

Semiconductor quantum dots (QDs) are a new class of fluorescent labels with broad applications in biomedical imaging, disease diagnostics, and molecular and cell biology. In comparison with organic dyes and fluorescent proteins, quantum dots have unique optical and electronic properties such as size-tunable light emission, improved signal brightness, resistance against photobleaching, and simultaneous excitation of multiple fluorescence colors. Recent advances have led to multifunctional nanoparticle probes that are highly bright and stable under complex in vitro and in vivo conditions. New designs involve encapsulating luminescent QDs with amphiphilic block copolymers, and linking the polymer coating to tumor-targeting ligands and drug-delivery functionalities. These improved QDs have opened new possibilities for real-time imaging and tracking of molecular targets in living cells, for multiplexed analysis of biomolecular markers in clinical tissue specimens, and for ultrasensitive imaging of malignant tumors in living animal models. In this article, we briefly discuss recent developments in bioaffinity QD probes and their applications in molecular profiling of individual cancer cells and clinical tissue specimens.

Xu, H. L., et al. (2018). "Glioma-Targeted Delivery of a Theranostic Liposome Integrated with Quantum Dots, Superparamagnetic Iron Oxide, and Cilengitide for Dual-Imaging Guiding Cancer Surgery." Adv Healthc Mater **7**(9): e1701130.

Herein, a theranostic liposome (QSC-Lip) integrated with superparamagnetic iron oxide nanoparticles (SPIONs) and quantum dots (QDs) and cilengitide (CGT) into one platform is constructed to target glioma under magnetic targeting (MT) for guiding surgical resection of glioma. Transmission electron microscopy and X-ray photoelectron spectroscopy confirm the complete coencapsulation of SPIONs and QDs in liposome. Besides, CGT is also effectively encapsulated into the liposome with an encapsulation efficiency of approximately 88.9%. QSC-Lip exhibits a diameter of 100 +/- 1.24 nm, zeta potential of -17.10 +/- 0.11 mV, and good stability in several mediums. Moreover, each cargo shows a biphasic release pattern from QSC-Lip, a rapid initial release within initial 10 h followed by a sustained release. Cellular uptake of QSC-Lip is significantly enhanced by C6 cells under MT. In vivo dual-imaging studies show that QSC-Lip not only produces an obvious negative-contrast enhancement effect on glioma by magnetic resonance imaging but also makes tumor emitting fluorescence under MT. The dual-imaging of QSC-Lip guides the accurate resection of glioma by surgery. Besides, CGT is also specifically distributed to glioma after administration of QSC-Lip under MT, resulting in an effective inhibition of tumors. The integrated liposome may be a potential carrier for theranostics of tumor.

Xu, J., et al. (2012). "Comparison of quantum dot technology with conventional immunohistochemistry in examining aldehyde dehydrogenase 1A1 as a potential biomarker for lymph node metastasis of head and neck cancer." Eur J Cancer **48**(11): 1682-1691.

This study explored whether the expression of aldehyde dehydrogenase 1 (ALDH1A1) in the primary tumour correlated with lymph node metastasis (LNM) of squamous cell carcinoma of the head and neck (HNSCC). We used both quantum dot (QD)-based immunohistofluorescence (IHF) and conventional immunohistochemistry (IHC) to quantify ALDH1A1 expression in primary tumour samples taken from 96 HNSCC patients, 50 with disease in the lymph nodes and 46 without. The correlation between the quantified level of ALDH1A1 expression and LNM in HNSCC patients was evaluated with univariate and multivariate analysis. The prognostic value of ALDH1A1 was

examined by Kaplan-Meier analysis and Wald test. ALDH1A1 was highly correlated with LNM in HNSCC patients ($p<0.0001$ by QD-based IHF and 0.039 by IHC). The two methods (QD-based IHF and conventional IHC) for quantification of ALDH1A1 were found to be comparable ($R=0.75$, $p<0.0001$), but QD-IHF was more sensitive and objective than IHC. The HNSCC patients with low ALDH1A1 expression had a higher 5-year survival rate than those with high ALDH1A1 level ($p=0.025$). Our study suggests that ALDH1A1 is a potential biomarker for predicting LNM in HNSCC patients, though it is not an independent prognostic factor for survival of HNSCC patients. Furthermore, QD-IHF has advantages over IHC in quantification of ALDH1A1 expression in HNSCC tissues.

Xu, J., et al. (2020). "Facile incorporation of DNA-templated quantum dots for sensitive electrochemical detection of the oral cancer biomarker interleukin-8." Anal Bioanal Chem **412**(11): 2599-2606.

Recent studies reveal a great value of interleukin-8 (IL-8), a pro-inflammatory cytokine, as a potent biomarker for early diagnosis of oral cancer. Herein, a new electrochemical method is proposed to detect IL-8 by facilely incorporating DNA-templated quantum dots (QDs). In principle, target IL-8 is first treated with the reducing agent tris(2-carboxyethyl)phosphine (TCEP) to yield active thiols and then captured by antibody-functionalized magnetic beads (MBs). Thereafter, via the Michael addition reaction between the active thiol and maleimide group, a maleimide-modified DNA probe is linked to the surface of MBs, which can initiate a process of rolling circle amplification. In this way, long-range DNA strands are generated on the MB surface, subsequently recruiting DNA-templated CdTe/CdS QDs (DNA-QDs) to act as electrochemical reporters. By tracing the responses of DNA-QDs, the method allows IL-8 detection in a linear range from 5 to 5000 fg/mL with a detection limit of 3.36 fg/mL. The selectivity, reproducibility, and applicability in complex serum samples are also demonstrated to be favorable, indicating that the method may have a great potential in the future. More importantly, the use of TCEP treatment in the method not only provides a facile way to incorporate DNA-QDs, avoiding the complicated and time-consuming preparation process of antibody-DNA conjugates or functional nanomaterials; but also makes the method capable of being extended to detect other protein biomarkers in view of widespread presence of disulfides, which may hold a broad potential to facilitate efficient biosensing designs.

Xu, N., et al. (2019). "Imaging of water soluble CdTe/CdS core-shell quantum dots in inhibiting multidrug resistance of cancer cells." Talanta **201**: 309-316.

Two different colors of water-soluble core-shell quantum dots CdTe/CdS (green and orange red) have been synthesized and characterized in this paper. The formation of core-shell quantum dots not only improves the fluorescence quantum yield, but also reduces the biological toxicity of quantum dots, and improves the fluorescence lifetime. Two novel fluorescent bioprobes, CdTe/CdS (lambdaem=545nm)-5-Fu and Bio-CdTe/CdS (lambdaem=600nm)-TAM, have been synthesized via the interaction of these two core-shell quantum dots with anticancer drugs (5-Fu) and P-gp inhibitors (TAM), respectively. These two fluorescent probes have been simultaneously used in fluorescence imaging of human breast cancer cells MDA-MB-231/MDR. It can be observed that under the action of P-gp inhibitors distributed on the cell membrane, anticancer drugs can be retained in cancer cells. According to the color of quantum dots on the probe, the visualization results of the action of anticancer drugs and P-gp inhibitors can be obtained. This study shows that to prepare functional bioprobes using core-shell quantum dots CdTe/CdS has great potential in the field of biomedical research such as anticancer drugs.

Xu, Q., et al. (2018). "Dual nanoenzyme modified microelectrode based on carbon fiber coated with AuPd alloy nanoparticles decorated graphene quantum dots assembly for electrochemical detection in clinic cancer samples." Biosens Bioelectron **107**: 153-162.

The development of high-efficient technologies for cancer biomarkers detection has attracted tremendous research effort for its great clinic significance. In this work, we designed a new type of flexible and robust nanohybrid microelectrode by modifying carbon fiber with dual nanoenzyme, i.e., AuPd alloy nanoparticles (AuPd-ANPs) decorated graphene quantum dots (GQDs) assembly, and explored its practical application in electrochemical sensing system for sensitive detection of cancer biomarker hydrogen peroxide (H2O2) in human breast cancer cells and tissue. For the preparation of dual nanoenzyme modified microelectrode, ionic liquid was used as the electrolyte for the effective electrodeposition of GQDs on carbon fiber substrate to form a close-packed assembly under a very negative potential, then the highly dense AuPd-ANPs were uniformly decorated on GQDs assembly by electrodeposition. In virtue of the structural merits and synergistic contribution of dual nanoenzyme in enhancing the electrocatalytic activity to H2O2, the resultant nanohybrid microelectrode exhibited good sensing performances for electrochemical detection of H2O2, including a high sensitivity of 371muAcm(-2) mM(-1), a wide linear

range from 1.0muM to 18.44mM, a low detection limit of 500nM (a signal-to-noise ratio of 3:1), as well as good selectivity and biocompatibility, which could be used for real-time tracking H2O2 released from different types of human breast cells and in situ sensitive detection of H2O2 in clinical breast cancer tissue.

Xu, W., et al. (2012). "Quantum dot-conjugated anti-GRP78 scFv inhibits cancer growth in mice." Molecules **17**(1): 796-808.

Semiconductor quantum dots (Qdots) have recently been shown to offer significant advantages over conventional fluorescent probes to image and study biological processes. The stability and low toxicity of QDs are well suited for biological applications. Despite this, the potential of Qdots remains limited owing to the inefficiency of existing delivery methods. By conjugating Qdots with small antibody fragments targeting membrane-bound proteins, such as GRP78, we demonstrate here that the Quantum dot- Anti-GRP78 scFv (Qdot-GRP78) retains its immunospecificity and its distribution can be monitored by visualization of multi-color fluorescence imaging both in vitro and in vivo. Moreover we demonstrate here for the first time that Qdot-GRP78 scFv bioconjugates can be efficiently internalized by cancer cells, thus upregulate phophosphate-AKT-ser473 and possess biological anti-tumour activity as shown by inhibition of breast cancer growth in a xenograft model. This suggests that nanocarrier-conjugated scFvs can be used as a therapeutic antibody for cancer treatment.

Yadav, P., et al. (2022). "Nontoxic Metal-Free Visible Light-Responsive Carbon Nitride Quantum Dots Cause Oxidative Stress and Cancer-Specific Membrane Damage." ACS Appl Bio Mater **5**(3): 1169-1178.

Graphitic carbon nitride (also known as g-CN or g-C3N4) has the intrinsic ability to generate electron-hole pairs under visible light illumination, resulting in the generation of reactive oxygen species (ROS). We report g-CN quantum dots (g-CNQDs) as a standalone photodynamic transducer for imparting significant oxidative stress in glioma cells, manifested by the loss of mitochondrial membrane potential. With an optimized treatment time, visible light source, and exposure window, the photodynamic treatment with g-CNQDs could achieve approximately 90% cancer cell death via apoptosis. The g-CNQDs, otherwise biocompatible with normal cells up to 5 mg/mL, showed approximately 20% necrotic cancer cell death in the absence of light due to membrane damage induced by a charge shielding effect at the acidic pH prevailing in the tumor environment. Acute toxicity analysis in C57BL/6 mice with intravenously injected g-CNQDs at a 20 mg/kg dose showed no signs of inflammatory response or organ damage.

Yan, X., et al. (2016). "CdSe/ZnS Quantum Dot-Labeled Lateral Flow Strips for Rapid and Quantitative Detection of Gastric Cancer Carbohydrate Antigen 72-4." Nanoscale Res Lett **11**(1): 138.

Carbohydrate antigen 72-4 (CA72-4) is an important biomarker associated closely with diagnosis and prognosis of early gastric cancer. How to realize quick, sensitive, specific, and quantitative detection of CA72-4 in clinical specimens has become a great requirement. Herein, we reported a CdSe/ZnS quantum dot-labeled lateral flow test strip combined with a charge-coupled device (CCD)-based reader was developed for rapid, sensitive, and quantitative detection of CA72-4. Two mouse monoclonal antibodies (mAbs) against CA72-4 were employed. One of them was coated as a test line, while another mAb was labeled with quantum dots and coated onto conjugate pad. The goat anti-mouse IgG was immobilized as a control line. After sample was added, a sandwich structure was formed with CA72-4 and these two mAbs. The fluorescent signal from quantum dots (QD)-labeled mAb in sandwich structure was related to the amount of detected CA72-4. A CCD-based reader was used to realize quantitative detection of CA72-4. Results showed that developed QD-labeled lateral flow strips to detect CA72-4 biomarker with the sensitivity of 2 IU/mL and 10 min detection time. One hundred sera samples from clinical patients with gastric cancer and healthy people were used to confirm specificity of this strip method; results showed that established strip method own 100 % reproducibility and 100 % specificity compared with Roche electrochemiluminescence assay results. In conclusion, CdSe/ZnS quantum dot-labeled lateral flow strips for detection of CA72-4 could realize rapid, sensitive, and specific detection of clinical samples and could own great potential in clinical translation in near future.

Yang, B., et al. (2019). "Double signal amplification strategy for ultrasensitive electrochemical biosensor based on nuclease and quantum dot-DNA nanocomposites in the detection of breast cancer 1 gene mutation." Biosens Bioelectron **142**: 111544.

Rapid and efficient detection of microRNA (miRNA) of breast cancer 1 gene mutation (BRCA1) at their earliest stages is one of the crucial challenges in cancer diagnostics. In this study, a highly-sensitive electrochemical DNA biosensor was fabricated by double signal amplification (DSA) strategy for the detection of ultra-trace miRNA of BRCA1. In the presence of target miRNA of BRCA1, the well-matched RNA-DNA duplexes were specifically recognized by double-strand specific nuclease (DSN), and the DNA part of the duplexes were then cleaved and miRNAs were released to trigger another following cycle, which

produced a primarily amplified signal by such a cyclic enzymatic signal amplification (CESA). Then triple-CdTe quantum dot labelled DNA nanocomposites (3-QD@DNA NC) was selectively hybridized with the cleaved DNA probe on the electrode and produced multiply amplified signals. The biosensor exhibited a high sensitivity for the detection of miRNA of BRCA1 in concentrations ranging from 5 aM to 5fM, and its detection limit of 1.2 aM was obtained, which is two or three orders of magnitude lower than those by single signal amplification strategy such as CESA or QD-labeled DNA probes. The as-prepared biosensor was successfully used to detect the miRNA of BRCA1 in human serum samples with acceptable stability, good reproducibility, and good recovery. The proposed DNA biosensor based on double signal amplification strategy provided a feasible, rapid, and sensitive platform for early clinical diagnosis and practical applications.

Yang, C., et al. (2019). "Biodegradable Polymer-Coated Multifunctional Graphene Quantum Dots for Light-Triggered Synergetic Therapy of Pancreatic Cancer." ACS Appl Mater Interfaces **11**(3): 2768-2781.

In this work, we reported the synthesis of an engineered novel nanocarrier composed of biodegradable charged polyester vectors (BCPVs) and graphene quantum dots (GQDs) for pancreatic cancer (MiaPaCa-2 cells) therapy applications. Such a nanocarrier was utilized to co-load doxorubicin (DOX) and small interfering ribonucleic acid (siRNA), resulting in the formation of GQD/DOX/BCPV/siRNA nanocomplexes. The resulting nanocomplexes have demonstrated high stability in physiologically mimicking media, excellent K-ras downregulation activity, and effective bioactivity inhibition for MiaPaCa-2 cells. More importantly, laser light was used to generate heat for the nanocomplexes via the photothermal effect to damage the cells, which was further employed to trigger the release of payloads from the nanocomplexes. Such triggered release function greatly enhanced the anticancer activity of the nanocomplexes. Preliminary colony formation study also suggested that GQD/DOX/BCPV/siRNA nanocomplexes are qualified carrier candidates in subsequent in vivo tests.

Yang, F., et al. (2013). "Microwave-assisted aqueous synthesis of new quaternary-alloyed CdSeTeS quantum dots; and their bioapplications in targeted imaging of cancer cells." Luminescence **28**(3): 392-400.

In this study, we report for the first time a one-pot approach for the synthesis of new CdSeTeS quaternary-alloyed quantum dots (QDs) in aqueous phase by microwave irradiation. CdCl2 was used as a Cd precursor during synthesis, NaHTe and NaHSe were used as Te and Se precursors and mercaptopropionic acid (MPA) was used as a stabilizer and source of sulfur. A series of quaternary-alloyed QDs of different sizes were prepared. CdSeTeS QDs exhibited a wide emission range from 549 to 709 nm and high quantum yield (QY) up to 57.7 %. Most importantly, the quaternary-alloyed QDs possessed significantly long fluorescence lifetimes > 100 ns as well as excellent photostability. Results of high-resolution transmission electron microscopy (HRTEM), energy dispersive X-ray spectroscopy (EDX) and powder X-ray diffraction (XRD) spectroscopy showed that the nanocrystals possessed a quaternary alloy structure with good crystallinity. Fluorescence correlation spectroscopy (FCS) showed that QDs possessed good water solubility and monodispersity in aqueous solution. Furthermore, CdSeTeS QDs were modified with alpha-thio-omega-carboxy poly(ethylene glycol) (HS-PEG-COOH) and the modified QDs were linked to anti-epidermal growth factor receptor (EGFR) antibodies. QDs with the EGFR antibodies as labeling probes were successfully applied to targeted imaging for EGFR on the surface of SiHa cervical cancer cells. We believe that CdSeTeS QDs can become useful probes for in vivo targeted imaging and clinical diagnosis.

Yang, L., et al. (2022). "High-sensitivity fluorescence detection for lung cancer CYFRA21-1 DNA based on accumulative hybridization of quantum dots." J Mater Chem B **10**(9): 1386-1392.

Sensitive detection of circulating tumor DNA (ctDNA) in vitro has attracted growing attention owing to its potential application in diagnostics of cancer. In this study, we synthesized hydrophilic AgInS2@ZnS core-shell quantum dot nanocrystals and magnetic Fe3O4 nanoparticles, and then the ctDNA triggered hybridization chain reaction was used to detect the CYFRA21-1 DNA associated with lung cancer. In the presence of CYFRA21-1 DNA, three hairpin structures were activated to turn on successively, resulting in the accumulation of quantum dots and eliciting considerable changes of the fluorescence signal. Compared with the conventional fluorescence detection, Fe3O4 provides magnetic adsorption properties and a large surface area for immobilizing and aggregating quantum dot nanoparticles attached to single-stranded DNA. The concentration of CYFRA21-1 is closely related to the number of quantum dots remaining after magnetic adsorption, which provides a promising approach for ctDNA quantification.

Yang, M., et al. (2013). "In situ energy transfer quenching of quantum dot electrochemiluminescence for sensitive detection of cancer biomarkers." Biosens Bioelectron **50**: 393-398.

In this work, we develop a sensitive and selective method for the detection of a cancer biomarker

(carcinoembryonic antigen, CEA) based on a new electrochemiluminescence (ECL) energy transfer mechanism, in which the energy transfer occurs from the excited quantum dots (QDs) to the in situ electro-generated quenchers. A CdTe QD-containing composite film is first deposited on the electrode followed by the conjugation of the primary antibody (Ab1) on the film. Subsequent incubation of the modified sensing electrode with CEA and the secondary antibody-alkaline phosphatase-gold nanoparticle labels (Ab2-ALP-AuNP) leads to the formation of the Ab1/CEA/Ab2-ALP-AuNPs immunocomplexes on the electrode surface. The captured ALP catalyzes the p-nitrophenyl phosphate disodium salt (p-NPP) substrate in the ECL detection buffer to p-nitrophenol (p-NP). The potential sweep on the electrode results in the oxidation of p-NP to p-benzoquinone (p-BQ) and the generation of excited QDs. The ECL emission of the excited QDs is therefore quenched through direct energy transfer from the excited QDs to p-BQ. This ECL quenching effect is significantly amplified because of the numerous ALP enzymes involved in each antibody-antigen recognition event. This proposed method of amplified quenching of QD ECL emission offers a low detection limit of 1.67 pg mL(-1) for CEA. In addition, this method exhibits high reproducibility and selectivity and can also be applied to serum samples. Given these advantages, this new ECL energy transfer approach holds great promise for the detection of other biological targets and has potential applications in clinical diagnoses.

Yang, X. Q., et al. (2011). "Quantum dot-based quantitative immunofluorescence detection and spectrum analysis of epidermal growth factor receptor in breast cancer tissue arrays." Int J Nanomedicine **6**: 2265-2273.

BACKGROUND: The epidermal growth factor receptor (EGFR) is a promising therapeutic target in cancer, but its clinical value in breast cancer remains controversial. Our previous studies have found that quantitative analysis of biomarkers with quantum dot-based nanotechnology had better detection performance than conventional immunohistochemistry. The present study was undertaken to investigate the prognostic value of EGFR in breast cancer using quantum dot-based quantitative spectral analysis. METHODS: EGFR expression in 65 breast cancer specimens was detected by immunohistochemistry and quantum dot-immunohistochemistry, and comparisons were made between the two methods. EGFR expression in tissue microarrays of 240 breast cancer patients was then detected by quantum dot-immunohistochemistry and spectral analysis. The prognostic value of EGFR immunofluorescence area (EGFR area) for five-year recurrence-free survival was investigated. RESULTS: The same antigen localization, high correlation of staining rates (r = 0.914), and high agreement of measurement (kappa = 0.848) of EGFR expression in breast cancer were found by quantum dot-immunohistochemistry and immunohistochemistry. The EGFR area showed significant differences by tumor grade, lymph node status, HER2 status, and hormone receptor status (all $P < 0.05$). Patients in the large EGFR area (>/= 30.51) group had a significantly higher five-year recurrence rate (47.2% versus 27.4%, P = 0.002) and worse five-year recurrence-free survival (log-rank test, P = 0.0015) than those in the small EGFR area (<30.51) group. In the subgroups, EGFR area was an independent prognosticator in the HER2-positive and lymph node-positive subgroups. CONCLUSION: Quantum dot-based quantitative detection demonstrates the prognostic value of EGFR area in the HER2-positive and lymph node-positive subgroups of invasive breast cancer.

Yang, Y., et al. (2017). "Hyaluronic Acid Conjugated Magnetic Prussian Blue@Quantum Dot Nanoparticles for Cancer Theranostics." Theranostics **7**(2): 466-481.

A multifunctional nanotheranostic agent was developed by conjugating both hyaluronic acid and bovine serum albumin coated CuInS2-ZnS quantum dots onto the surface of magnetic Prussian blue nanoparticles. The obtained nanoagent could serve as an efficient contrast agent to simultaneously enhance near infrared (NIR) fluorescence and magnetic resonance (MR) imaging greatly. The coexistence of magnetic core and CD44 ligand hyaluronic acid was found to largely improve the specific uptake of the nanoagent by CD44 overexpressed HeLa cells upon applying an external magnetic field. Both NIR fluorescence and MR imaging in vivo proved high accumulation of the nanoagent at tumor site due to its excellent CD44 receptor/magnetic dual targeting capability. After intravenous injection of the nanoagent and treatment of external magnetic field, the tumor in nude mice was efficiently ablated upon NIR laser irradiation and the tumor growth inhibition was more than 89.95%. Such nanotheranostic agent is of crucial importance for accurately identifying the size and location of the tumor before therapy, monitoring the photothermal treatment procedure in real-time during therapy, assessing the effectiveness after therapy.

Yang, Y., et al. (2021). "Graphene Quantum Dots for Molecular Radiotherapy: Radiolabeled Graphene Quantum Dots with Radium ((223)Ra) Showed Potent Effect Against Bone Cancer." J Biomed Nanotechnol **17**(9): 1858-1865.

The necessity of new drugs with special attention for the therapy of cancer is increasing each day. Despite their properties, alpha therapeutic radiopharmaceuticals, especially based on the use of radium ((223)Ra) are good choices, due to the highest

and differential cytotoxicity, low adverse effects, and higher bioaccumulation on tumor sites. The use of graphene quantum dots as the carrier for (223)Ra is a promising approach since graphene quantum dots has low toxicity, high biocompatibility, and adequate size for tumor penetration. In this study, we developed, characterized, radiolabeled with (223)Ra, and evaluated in vitro and in vivo graphene quantum dots radiolabeled with radium ((223)Ra) for bone cancer. The results showed that (223)Ra is incorporated into the graphene quantum dot following the Fajans-Paneth-Hahn Law. The cell viability showed a potent effect on osteosarcoma cells (MG63 and SAOS2) but a lower effect in normal fibroblast cells (hFB), corroborating the preferential targeting. Also, the results showed a more prominent effect on MG63 than SAOS2 cells, corroborating the targeting for more undifferentiated cells. The in vivo results demonstrated a renal excretion, associated with fecal excretion and accumulation in bone. The results corroborate the efficacy of (223)RaGQDs and open new perspectives for the use of use (223)RaGQDs, in several other diseases.

Yang, Y., et al. (2020). "Enhanced imaging of glycan expressing cancer cells using poly(glycidyl methacrylate)-grafted silica nanospheres labeled with quantum dots." Anal Chim Acta **1095**: 138-145.

Glycosylation on the cell surface contains abundant biological information, and detecting the glycan on cell surfaces can offer critical insight into biology and diseases. Here, a signal amplification strategy for the sensitive detection of glycan expression on the cell surface was proposed. In this approach, glycans on the cell surface were detected with poly(glycidyl methacrylate)-grafted silica nanosphere labeled with quantum dots (QDs) and biotin through the specific affinity reaction of avidin-biotin on the cancer cells. Glycans on the cell surface were first labeled via selective oxidization of sialyl groups into aldehydes by periodate. Aniline-catalyzed hydrazone ligation with biotin hydrazide was then used for the specific recognition to avidin. The nanoprobe was fabricated with "living" SiO2 nanoparticles with alkyl bromide groups on their surfaces. They were then subsequently grafted with poly(glycidyl methacrylate) (PGMA) brushes via the successive surface-initiated atom transfer radical polymerization. The CdTe QDs and biotin were immobilized through a ring-open reaction with epoxy groups in the PGMA brushes to obtain QDs/biotin-polymer brush-functionalized silica nanosphere (SiO2-PGMA-QDs/biotin). Enhanced sensitivity could be achieved by an increase in CdTe QDs loading per assay event, because of the large number of surface functional epoxy groups offered by the PGMA. As a result, fluorescence signal increased versus the unamplified method. This method successfully demonstrates a simple, specific, and potent method to detect glycans on the cell surface.

Yao, L., et al. (2022). "Carbon Quantum Dots-Based Nanozyme from Coffee Induces Cancer Cell Ferroptosis to Activate Antitumor Immunity." ACS Nano **16**(6): 9228-9239.

Carbon quantum dots (CQDs) offer huge potential due to their enzymatic properties as compared to natural enzymes. Thus, discovery of CQDs-based nanozymes with low toxicity from natural resources, especially daily food, implies a promising direction for exploring treatment strategies for human diseases. Here, we report a CQDs-based biocompatible nanozyme prepared from chlorogenic acid (ChA), a major bioactive natural product from coffee. We found that ChA CQDs exhibited obvious GSH oxidase-like activities and subsequently promoted cancer cell ferroptosis by perturbation of GPX4-catalyzed lipid repair systems. In vivo, ChA CQDs dramatically suppressed the tumor growth in HepG2-tumor-bearing mice with negligible side toxicity. Particularly, in hepatoma H22-bearing mice, ChA CQDs recruited massive tumor-infiltrating immune cells including T cells, NK cells, and macrophages, thereby converting "cold" to "hot" tumors for activating systemic antitumor immune responses. Taken together, our study suggests that natural product-derived CQDs from coffee can serve as biologically safe nanozymes for anticancer therapeutics and may aid the development of nanotechnology-based immunotherapeutic.

Yao, X., et al. (2017). "Mesoporous Silica Nanoparticles Capped with Graphene Quantum Dots for Potential Chemo-Photothermal Synergistic Cancer Therapy." Langmuir **33**(2): 591-599.

In this study, mesoporous silica nanoparticles (MSNs) have been successfully capped with graphene quantum dots (GQDs) to form multifunctional GQD-MSNs with the potential for synergistic chemo-photothermal therapy. The structure, drug-release behavior, photothermal effect, and synergistic therapeutic efficiency of GQD-MSNs to 4T1 breast cancer cells were investigated. The results showed that GQD-MSNs were monodisperse and had a particle size of 50-60 nm. Using doxorubicin hydrochloride (DOX) as a model drug, the DOX-loaded GQD-MSNs (DOX-GQD-MSNs) not only exhibited pH- and temperature-responsive drug-release behavior, but using near-infrared irradiation, they efficiently generated heat to kill cancer cells. Furthermore, GQD-MSNs were biocompatible and were internalized by 4T1 cells. Compared with chemotherapy and photothermal therapy alone, DOX-GQD-MSNs were much more effective in killing the 4T1 cells owing to a synergistic chemo-

photothermal effect. Therefore, GQD-MSNs may have promising applications in cancer therapy.

Yin, N., et al. (2018). "Tunable excitation properties of ZnCdS:Mn/ZnS quantum dots for cancer imaging." Luminescence **33**(3): 630-635.

Water-soluble ZnS:Mn quantum dots (QDs) were synthesized using a hydrothermal method with 3-mercaptopropionic acid as stabilizer. The optical properties of ZnS:Mn QDs were thoroughly investigated by tuning the doping concentration of Mn(2+) and the Zn/S precursor ratio, to obtain an optimal parameter for QDs with excellent fluorescence characteristics. ZnS:Mn QDs excited at only one wavelength, however, which seriously limited their further application. Here, a trace Cd ion was doped into a ZnS host, resulting in QD excitation covering a wide adjustable waveband. Furthermore, when a ZnS shell was coated onto the surface of the ZnCdS:Mn QDs, photoluminescence intensity and stability were further enhanced. After coupling with an anti-CK 19 antibody, the ZnCdS:Mn/ZnS core/shell QDs were able to function by labeling cancer cells, indicating that they could be considered as a suitable bio-probe for cells and tissue imaging.

Yong, K. T. (2009). "Mn-doped near-infrared quantum dots as multimodal targeted probes for pancreatic cancer imaging." Nanotechnology **20**(1): 015102.

This work presents a novel approach to producing manganese (Mn)-doped quantum dots (Mnd-QDs) emitting in the near-infrared (NIR). Surface functionalization of Mnd-QDs with lysine makes them stably disperse in aqueous media and able to conjugate with targeting molecules. The nanoparticles were structurally and compositionally characterized and maintained a high photoluminescence quantum yield and displayed paramagnetism in water. The receptor-mediated delivery of bioconjugated Mnd-QDs into pancreatic cancer cells was demonstrated using the confocal microscopy technique. Cytotoxicity of Mnd-QDs on live cells has been evaluated. The NIR-emitting characteristic of the QDs has been exploited to acquire whole animal body imaging with high contrast signals. In addition, histological and blood analysis of mice have revealed that no long-term toxic effects arise from MnD-QDs. These studies suggest multimodal Mnd-QDs have the potentials as probes for early pancreatic cancer imaging and detection.

Yong, K. T. (2010). "Biophotonics and biotechnology in pancreatic cancer: cyclic RGD-peptide-conjugated type II quantum dots for in vivo imaging." Pancreatology **10**(5): 553-564.

This work introduces a novel, facile and straightforward approach to produce cyclic-RGD-peptide-conjugated type II CdTe/CdS quantum dot (QD) formulation for pancreatic tumor targeting and imaging in live animals. The ultra-small QDs were prepared by a hot colloidal synthesis method. Phospholipid micelles were then used to encapsulate the QDs, allowing them to be stably dispersed in biological fluids and able to conjugate with cyclic-RGD peptides. The QD complex had shown low cytotoxicity on Panc-1 human pancreatic cancer cell lines. In addition, the tissue sections and biodistribution of QD complexes were imaged and analyzed in mice bearing pancreatic tumor xenografts, confirming specific tumor targeting. These studies support further evaluation of type II QDs as potential probes for early pancreatic cancer assessment and detection.

Yong, K. T., et al. (2009). "Imaging pancreatic cancer using bioconjugated InP quantum dots." ACS Nano **3**(3): 502-510.

In this paper, we report the successful use of non-cadmium-based quantum dots (QDs) as highly efficient and nontoxic optical probes for imaging live pancreatic cancer cells. Indium phosphide (core)-zinc sulfide (shell), or InP/ZnS, QDs with high quality and bright luminescence were prepared by a hot colloidal synthesis method in nonaqueous media. The surfaces of these QDs were then functionalized with mercaptosuccinic acid to make them highly dispersible in aqueous media. Further bioconjugation with pancreatic cancer specific monoclonal antibodies, such as anticlaudin 4 and antiprostate stem cell antigen (anti-PSCA), to the functionalized InP/ZnS QDs, allowed specific in vitro targeting of pancreatic cancer cell lines (both immortalized and low passage ones). The receptor-mediated delivery of the bioconjugates was further confirmed by the observation of poor in vitro targeting in nonpancreatic cancer based cell lines which are negative for the claudin-4-receptor. These observations suggest the immense potential of InP/ZnS QDs as non-cadmium-based safe and efficient optical imaging nanoprobes in diagnostic imaging, particularly for early detection of cancer.

Yong, K. T., et al. (2007). "Quantum rod bioconjugates as targeted probes for confocal and two-photon fluorescence imaging of cancer cells." Nano Lett **7**(3): 761-765.

Live cell imaging using CdSe/CdS/ZnS quantum rods (QRs) as targeted optical probes is reported. The QRs, synthesized in organic media using a binary surfactant mixture, were dispersed in aqueous media using mercaptoundecanoic acid (MUA) and lysine. Transferrin (Tf) was linked to the QRs to produce QR-Tf bioconjugates that were used for targeted in vitro delivery to a human cancer cell line. Confocal and two-photon imaging were used to confirm receptor-mediated

uptake of QR-Tf conjugates into the HeLa cells, which overexpress the transferrin receptor (TfR). Uptake was not observed with QRs that lacked Tf functionalization or with cells that were presaturated with free Tf and then treated with Tf-functionalized QRs.

Yu, X., et al. (2013). "On-chip dual detection of cancer biomarkers directly in serum based on self-assembled magnetic bead patterns and quantum dots." Biosens Bioelectron **41**: 129-136.

A sandwich immunoassay method for rapid detection of dual cancer biomarkers in serum on a magnetic field controllable microfluidic chip (MFCM-Chip) was established. A nickel pattern was used to generate high magnetic field gradients to increase the magnetic force on the superparamagnetic beads (SPMBs), which enabled the rapid generation of controllable SPMB patterns in microfluidic channels. The SPMB patterns could keep stable during the fast continuous washing process even at a flow rate of 50 muL/min. This approach demonstrated excellent specificity because the fast continuous washing could remove non-specifically adsorptive contaminants more efficiently than fixed volume batch washing. This approach was used to simultaneously detect carcinoma embryonic antigen (CEA) and alpha-fetoprotein (AFP) directly in serums. The whole on-chip detection was finished within 40 min, which was much faster than conventional enzyme-linked immunosorbent assay (ELISA) method. High luminescent streptavidin modified QDs (SA-QDs) were used as fluorescence indicators, and the detection limits were 3.5 ng/mL and 3.9 ng/mL for CEA and AFP, respectively. The linear ranges were from 10.0 ng/mL to 800.0 ng/mL. With the high sensitivity, high selectivity and short assay time, this approach could be used for rapid, high throughput detection of cancer biomarkers in clinical trials.

Yu, Y., et al. (2012). "Hydrothermal synthesis of GSH-TGA co-capped CdTe quantum dots and their application in labeling colorectal cancer cells." Colloids Surf B Biointerfaces **95**: 247-253.

We have successfully synthesized GSH and TGA co-capped CdTe quantum dots (QDs) with good biological compatibility and high fluorescence intensity. The effects of different reaction time, temperature, pH value, ligand concentration and the molar ratio of GSH/TGA were carefully investigated to optimize the synthesis condition. The optical properties of as-prepared CdTe QDs were studied by UV-visible absorption spectrum and fluorescence spectrum, meanwhile their structure and morphology were characterized using transmission electron microscope (TEM), Fourier transform infrared spectra (FT-IR) and X-ray powder diffraction (XRD). Compared with the CdTe QDs that are single-capped with either GSH or TGA, the GSH-TGA co-capped CdTe QDs demonstrated significantly improved fluorescence intensity and optical stability. In addition, GSH-TGA co-capped CdTe QDs were conjugated to amonoclonal antibody ND-1. The GSH-TGA co-capped CdTe QDs-antibody probe was successfully used to label colorectal cancer cells, CCL187, in vitro.

Yuan, J. P., et al. (2015). "Quantum dots-based quantitative and in situ multiple imaging on ki67 and cytokeratin to improve ki67 assessment in breast cancer." PLoS One **10**(4): e0122734.

BACKGROUND: As a marker for tumor cell proliferation, Ki67 has important impacts on breast cancer (BC) prognosis. Although immunohistochemical staining is the current standard method, variations in analytical practice make it difficult for pathologists to manually measure Ki67 index. This study was to develop a fluorescent spectrum-based quantitative analysis of Ki67 expression by quantum-dots (QDs) multiple imaging technique. METHODS: A QDs-based in situ multiple fluorescent imaging method was developed, which stained nuclear Ki67 as red signal and cytoplasmic cytokeratin (CK) as green signal. Both Ki67 and CK signals were automatically separated and quantified by professional spectrum analysis software. This technique was applied to tissue microarrays from 240 BC patients. Both Ki67 and CK values, and Ki67/CK ratio were obtained for each patient, and their prognostic value on 5-year disease free survival was assessed. RESULTS: This method simultaneously stains nuclear Ki67 and cytoplasmic CK with clear signal contrast, making it easy for signal separation and quantification. The total fluorescent signal intensities of both Ki67 sum and CK sum were obtained, and Ki67/CK ratio calculated. Ki67 sum and Ki67/CK ratio were each attributed into two grades by X-tile software based on the best P value principle. Multivariate analysis showed Ki67 grade (P = 0.047) and Ki67/CK grade (P = 0.004) were independent prognostic factors. Furthermore, area under curve (AUC) of ROC analysis for Ki67/CK grade (AUC: 0.683, 95%CI: 0.613-0.752) was higher than Ki67 grade (AUC: 0.665, 95%CI: 0.596-0.734) and HER-2 gene (AUC: 0.586, 95%CI: 0.510-0.661), but lower than N stage (AUC: 0.760, 95%CI: 0.696-0.823) and histological grade (AUC: 0.756, 95%CI: 0.692-0.820) on predicting the risk for recurrence. CONCLUSIONS: A QDs-based quantitative and in situ multiple imaging on Ki67 and CK was developed to improve Ki67 assessment in BC, and Ki67/CK grade had better performance than Ki67 grade in predicting prognosis.

Yuan, R., et al. (2018). "Quantum dot-based fluorescent probes for targeted imaging of the EJ human bladder

urothelial cancer cell line." Exp Ther Med **16**(6): 4779-4783.

QDs are a type of inorganic nanoparticle with unique optical properties. As a fluorescent label, QDs are widely used in biomedical fields. In the present study, fluorescent probes of quantum dots (QDs) conjugated with a prostate stem cell antigen (PSCA) monoclonal antibody (QD-PSCA) were prepared to study the targeted imaging of QD-PSCA probes in EJ human bladder urothelial cancer cells and analyze the feasibility of QD-based non-invasive tumor-targeted imaging in vivo. QDs with an emission wavelength of 605 nm (QD605) were conjugated with PSCA to prepare QD605-PSCA fluorescent probes by chemical covalent coupling. The optical properties of the probes coupled and uncoupled with PSCA were measured and assessed using an ultraviolet spectrophotometer and a fluorescence spectrophotometer. Direct immune-fluorescent labeling was utilized to detect and analyze imaging of the probes for EJ cells. The results revealed that QD605-PSCA probes retained the fluorescent properties of QD605 and the immunogenicity of the PSCA protein. The probes were able to specifically recognize the PSCA protein expressed in bladder cancer cells, while fluorescence was stable and had a long duration. The present study suggests that QD-PSCA fluorescent probes may be useful for specific targeted labeling and imaging in bladder urothelial cancer cells. Furthermore, the probes possess good optical stability and may be useful for research into non-invasive targeted imaging, early diagnosis and targeted in vivo tumor therapy.

Zajac, A., et al. (2007). "Protein microarrays and quantum dot probes for early cancer detection." Colloids Surf B Biointerfaces **58**(2): 309-314.

We describe here a novel approach for detection of cancer markers using quantum dot protein microarrays. Both relatively new technologies; quantum dots and protein microarrays, offer very unique features that together allow detection of cancer markers in biological specimens (serum, plasma, body fluids) at pg/ml concentration. Quantum dots offer remarkable photostability and brightness. They do not exhibit photobleaching common to organic fluorophores. Moreover, the high emission amplitude for QDs results in a marked improvement in the signal to noise ratio of the final image. Protein microarrays allow highly parallel quantitation of specific proteins in a rapid, low-cost and low sample volume format. Furthermore the multiplexed assay enables detection of many proteins at once in one sample, making it a powerful tool for biomarker analysis and early cancer diagnostics. In a series of multiplexing experiments we investigated ability of the platform to detect six different cytokines in protein solution. We were able to detect TNF-alpha, IL-8, IL-6, MIP-1beta, IL-13 and IL-1beta down to picomolar concentration, demonstrating high sensitivity of the investigated detection system. We have also constructed and investigated two different models of quantum dot probes. One by conjugation of nanocrystals to antibody specific to the selected marker--IL-10, and the second by use of streptavidin coated quantum dots and biotinylated detector antibody. Comparison of those two models showed better performance of streptavidin QD-biotinylated detector antibody model. Data quantitated using custom designed computer program (CDAS) show that proposed methodology allows monitoring of changes in biomarker concentration in physiological range.

Zaman, M. B., et al. (2011). "Single-domain antibody bioconjugated near-IR quantum dots for targeted cellular imaging of pancreatic cancer." J Nanosci Nanotechnol **11**(5): 3757-3763.

Successful targeted imaging of BxPC3 human pancreatic cancer cells is feasible with near-IR CdTeSe/CdS quantum dots (QDs) functionalized with single-domain antibody (sdAb) 2A3. For specific targeting, sdAbs are superior to conventional antibodies, especially in terms of stability, aggregation, and production cost. The bright CdTeSe/CdS QDs were synthesized to emit in the diagnostic window of 650-900 nm with a narrow emission band. 2A3 was derived from llama and is small in size of 13 kDa, but with fully-functional recognition to the target carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), a possible biomarker as a therapeutic target of pancreatic cancer. For compelling imaging, optical may be the most sensible among the various imaging modalities, regarding the sensitivity and cost. This first report on sdAb-conjugated near-IR QDs with high signal to background sensitivity for targeted cellular imaging brings insights into the development of optical molecular imaging for early stage cancer diagnosis.

Zdobnova, T. A., et al. (2012). "Self-assembling complexes of quantum dots and scFv antibodies for cancer cell targeting and imaging." PLoS One **7**(10): e48248.

Semiconductor quantum dots represent a novel class of fluorophores with unique physical and chemical properties which could enable a remarkable broadening of the current applications of fluorescent imaging and optical diagnostics. Complexes of quantum dots and antibodies are promising visualising agents for fluorescent detection of selective biomarkers overexpressed in tumor tissues. Here we describe the construction of self-assembling fluorescent complexes of quantum dots and anti-HER1 or anti-HER2/neu scFv antibodies and their interactions with cultured tumor cells. A binding strategy based on a very specific non-

covalent interaction between two proteins, barnase and barstar, was used to connect quantum dots and the targeting antibodies. Such a strategy allows combining the targeting and visualization functions simply by varying the corresponding modules of the fluorescent complex.

Zhang, F., et al. (2018). "Rapid aqueous synthesis of CuInS/ZnS quantum dots as sensor probe for alkaline phosphatase detection and targeted imaging in cancer cells." Talanta **189**: 411-417.

Early diagnosis of chronic, critical diseases improves clinical outcomes, and biomarkers play an important role as an indicator of severity or presence of a disease. Alkaline phosphatase (ALP) is one such vital biomarker in the diagnosis of several diseases. Herein we introduce a facile, sensitive fluorescent assay, based on the inner filter effect (IFE), for ALP activity determination in serum and in living cells. It is well known that the key to maximize the sensitivity of an IFE-based fluorescence assays is to broaden the overlap between the absorption of an absorber and the excitation/emission of a fluorophore. We employed CuInS/ZnS quantum dots (CIS/ZnS QDs) and p-nitrophenylphosphate (PNPP) as the fluorescent indicator and the substrate, respectively, for ALP activity assessment. Due to the CIS/ZnS QDs have an efficient excitation at 405nm, meanwhile with a large Stokes shift emission at 588nm, p-nitrophenol (PNP) with absorption peak at 405nm, the hydrolyzed produce of PNPP and ALP, can act as a competitive absorber to absorb the excitation light of CIS/ZnS QDs, resulting in noticeable quenching of CIS/ZnS QDs. The proposed sensor detects ALP activity in human serum samples (sample consumption: 20muL) with detection limit of 0.01UL(-1). Excellent biocompatibility of CIS/ZnS QDs enables the sensor to monitor endogenous ALP in living cells. Furthermore, because the surface modification or the linking between the receptor and the fluorophore is no longer required, this fluorescent sensing system has the potential to simplify ALP clinical measurement, thereby improving diagnostics of relevant diseases.

Zhang, H., et al. (2020). "Graphene Quantum Dot-Based Nanocomposites for Diagnosing Cancer Biomarker APE1 in Living Cells." ACS Appl Mater Interfaces **12**(12): 13634-13643.

As an essential DNA repair enzyme, apurinic/apyrimidinic endonuclease 1 (APE1) is overexpressed in most human cancers and is identified as a cancer diagnostic and predictive biomarker for cancer risk assessment, diagnosis, prognosis, and prediction of treatment efficacy. Despite its importance in cancer, however, it is still a significant challenge nowadays to sense abundance variation and monitor enzymatic activity of this biomarker in living cells. Here, we report our construction of biocompatible functional nanocomposites, which are a combination of meticulously designed unimolecular DNA and fine-sized graphene quantum dots. Upon utilization of these nanocomposites as diagnostic probes, massive accumulation of fluorescence signal in living cells can be triggered by merely a small amount of cellular APE1 through repeated cycles of enzymatic catalysis. Most critically, our delicate structural designs assure that these graphene quantum dot-based nanocomposites are capable of sensing cancer biomarker APE1 in identical type of cells under different cell conditions and can be applied to multiple cancerous cells in a highly sensitive and specific manners. This work not only brings about new methods for cytology-based cancer screening but also lays down a general principle for fabricating diagnostic probes that target other endogenous biomarkers in living cells.

Zhang, H., et al. (2013). "Microfluidic beads-based immunosensor for sensitive detection of cancer biomarker proteins using multienzyme-nanoparticle amplification and quantum dots labels." Biosens Bioelectron **42**: 23-30.

This study reports the development of a microfluidic beads-based immunosensor for sensitive detection of cancer biomarker alpha-fetoprotein (AFP) that uses multienzyme-nanoparticle amplification and quantum dots labels. This method utilizes microbeads functionalized with the capture antibodies (Ab(1)) and modified electron rich proteins as sensing platform that was fabricated within a microfluidic channel, and uses gold nanoparticles (AuNPs) functionalized with the horseradish peroxidase (HRP) and the detection antibodies (Ab(2)) as label. Greatly enhanced sensitivity for the cancer biomarker is based on a dual signal amplification strategy: first, the large surface area of Au nanoparticle carrier allows several binding events of HRP on each nanosphere. Enhanced sensitivity was achieved by introducing the multi-HRP-antibody functionalized AuNPs onto the surface of microbeads through "sandwich" immunoreactions and subsequently multiple biotin moieties could be deposited onto the surface of beads resulted from the oxidation of biotin-tyramine by hydrogen peroxide. Streptavidin-labeled quantum dots were then allowed to bind to the deposited biotin moieties and displayed the signal. Secondly, enhanced mass transport capability inherent from microfluidics leads to higher capture efficiency of targets because continuous flow within micro-channel delivers fresh analyte solution to the reaction site which maintains a high concentration gradient differential to enhance mass transport. Based on the dual signal amplification strategy, the developed microfluidic bead-based immunosensor could discriminate as low as 0.2 pg mL(-)(1) AFP in 10 muL of undiluted calf serum (0.2

fg/chip), and showed a 500-fold increase in detection limit compared to the off-chip test and 50-fold increase in detection limit compared to microfluidic beads-based immunoassay using single label HRP-Ab(2). The immunosensor showed acceptable repeatability and reproducibility. This microfluidic beads-based immunosensor is a promising platform for disease-related biomolecules at the lowest level at their earliest incidence.

Zhang, H., et al. (2009). "Detection and downregulation of type I IGF receptor expression by antibody-conjugated quantum dots in breast cancer cells." Breast Cancer Res Treat **114**(2): 277-285.

The type I insulin-like growth factor (IGF) receptor (IGF1R) is a transmembrane tyrosine kinase involved in breast cancer proliferation, survival, and metastasis. Several monoclonal antibodies directed against the receptor are in clinical trials. In order to develop a methodology to detect and measure IGF1R levels in breast cancer cells, we covalently conjugated an IGF1R antibody, AVE-1642, with quantum dots (Qdots), which are nanocrystals that emit fluorescence upon excitation. AVE-1642 Qdots only bound to cells that express IGF1R, and measured IGF1R levels by fluorescence emission at 655 nm. After binding to the cell surface, AVE-1642 Qdots underwent receptor mediated endocytosis, localized to endosome, and later translocated into the nucleus. Treating MCF-7 cells with AVE-1642 Qdots, but not unconjugated Qdots alone, downregulated IGF1R levels and rendered cells refractory to IGF-I stimulation. Furthermore, cell proliferation was slightly inhibited by AVE-1642 Qdots, but not the unconjugated Qdots. Our data suggest that AVE-1642 Qdots can be used to detect IGF1R expression and measure changes in cell surface receptor levels. In addition, the inhibitory effect of AVE-1642 Qdots to cell proliferation implies that it may serve as a traceable therapeutic agent.

Zhang, H., et al. (2008). "Quantum dots for cancer diagnosis and therapy: biological and clinical perspectives." Nanomedicine (Lond) **3**(1): 83-91.

Quantum dots (QDs) are semiconductor nanocrystals that emit fluorescence on excitation with a light source. They have excellent optical properties, including high brightness, resistance to photobleaching and tunable wavelength. Recent developments in surface modification of QDs enable their potential application in cancer imaging. QDs with near-infrared emission could be applied to sentinel lymph-node mapping to aid biopsy and surgery. Conjugation of QDs with biomolecules, including peptides and antibodies, could be used to target tumors in vivo. In this review, we summarize recent progress in developing QDs for cancer diagnosis and treatment from a clinical standpoint and discuss future prospects of further improving QD technology to identify metastatic cancer cells, quantitatively measure the level of specific molecular targets and guide targeted cancer therapy by providing biodynamic markers for target inhibition.

Zhang, H., et al. (2018). "Label-free fluorescence imaging of cytochrome c in living systems and anti-cancer drug screening with nitrogen doped carbon quantum dots." Nanoscale **10**(11): 5342-5349.

As an important biomarker for the early stage of apoptosis, cytochrome c (Cyt c) has been recognized as a key component of the intrinsic apoptotic pathway. Fluorescence imaging tools enabling detection of Cyt c in apoptotic signaling have been rarely explored, though they are critical for cell biology and clinical theranostics. Here, we designed a novel label-free N-doped carbon dot (N-doped CD)-based nanosensor that enables fluorescence activation imaging of Cyt c release in cell apoptosis. The inner filter effect of Cyt c towards N-doped CDs enabled quantitative Cyt c measurement. The nanosensor exhibited high sensitivity and selectivity, rapid response, good cell-membrane permeability and low cytotoxicity. All these features are favorable for in situ visualization of Cyt c for apoptosis research. Notably, the developed nanosensor was successfully applied to monitor intracellular release of Cyt c, and to visualize Cyt c in living zebrafish for the first time. Moreover, it also provided a viable platform for cell-based screening of apoptosis-inducing compounds. In virtue of these advantages and potential, the developed assay not only holds great significance for the better understanding of certain diseases at the cellular level, but also provides an invaluable platform for apoptotic studies and screening of anti-cancer drugs toward drug development.

Zhang, J., et al. (2010). "Fluorescent quantum dot-labeled aptamer bioprobes specifically targeting mouse liver cancer cells." Talanta **81**(1-2): 505-509.

Fluorophore-labeled bioprobes are the key for fluorescent-labeled imaging technology. In the present work, mouse liver hepatoma cell line BNL 1ME A.7R.1 (MEAR)-specific ssDNA aptamer TLS9a was used to fabricate quantum dot-labeled aptamer bioprobe (QD-Apt), which was obtained by conjugating streptavidin-modified quantum dots (SA-QDs) with biotin-derived aptamer via the interaction between biotin and streptavidin. The QD-Apt was of monodispersity and excellent fluorescence properties. When the optimum ratio of SA-QDs to aptamer, which is 1:16, was used in the preparation of the QD-Apt, the resultant QD-Apt was of satisfactory bioactivity. They could specifically recognize MEAR cells and could not recognize BNL cells and Hela cells. Particularly, the growth and viability of QD-Apt bound MEAR cells were not

affected by QD-Apt within 84 h compared to control cells, indicating that the probe was biocompatible and suitable for live cell imaging.

Zhang, L., et al. (2018). "In vivo tumor active cancer targeting and CT-fluorescence dual-modal imaging with nanoprobe based on gold nanorods and InP/ZnS quantum dots." J Mater Chem B **6**(17): 2574-2583.

In this paper, gold nanorods and InP/ZnS quantum dots were encapsulated together in a silica medium, and the targeting molecular peptide c(RGDfC) was further connected after surface modification with PEG and PEG derivatives to prepare a multifunctional Au@QD@SiO2/PEG-c(RGDfC) probe. Dynamic Light Scattering showed that the probe size was about 215.01 +/- 2.72 nm, and its dispersibility was good. In in vitro experiments when the concentration was as high as 200 mug mL(-1), the activity of the cells was still 85% due to low toxicity. In vivo experiments showed that the probe had excellent tumor targeting, X-ray computed tomography (CT) imaging and fluorescence imaging capabilities. The experiments revealed that the probe had a long blood circulation time (T1/2 = 7.78 h) in mice. Biochemical analysis, liver enzyme analysis and histomorphological analysis after probe injection showed that the probe had no obvious side effects on the normal functions of the main organs, indicating good biosafety. In vivo imaging experiments showed that 6 d after intravenous injection, the tumor sites of a HeLa tumor-bearing nude mice positive group presented obvious fluorescence and CT signals, indicating that the prepared nanoprobe had good tumor targeting dual-mode imaging capabilities and therefore showed great potential in biomedical imaging applications, especially the diagnosis of cancer.

Zhang, M., et al. (2022). "Intracellular Trafficking and Distribution of Cd and InP Quantum Dots in HeLa and ML-1 Thyroid Cancer Cells." Nanomaterials (Basel) **12**(9).

The study of the interaction of engineered nanoparticles, including quantum dots (QDs), with cellular constituents and the kinetics of their localization and transport, has provided new insights into their biological consequences in cancers and for the development of effective cancer therapies. The present study aims to elucidate the toxicity and intracellular transport kinetics of CdSe/ZnS and InP/ZnS QDs in late-stage ML-1 thyroid cancer using well-tested HeLa as a control. Our XTT (2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide) viability assay (Cell Proliferation Kit II) showed that ML-1 cells and non-cancerous mouse fibroblast cells exhibit no viability defect in response to these QDs, whereas HeLa cell viability decreases. These results suggest that HeLa cells are more sensitive to the QDs compared to ML-1 cells. To test the possibility that transporting rates of QDs are different between HeLa and ML-1 cells, we performed a QD subcellular localization assay by determining Pearson's Coefficient values and found that HeLa cells showed faster QDs transporting towards the lysosome. Consistently, the ICP-OES test showed the uptake of CdSe/ZnS QDs in HeLa cells was significantly higher than in ML-1 cells. Together, we conclude that high levels of toxicity in HeLa are positively correlated with the traffic rate of QDs in the treated cells.

Zhang, M., et al. (2018). "Black Phosphorus Quantum Dots Gated, Carbon-Coated Fe3 O4 Nanocapsules (BPQDs@ss-Fe3O4@C) with Low Premature Release Could Enable Imaging-Guided Cancer Combination Therapy." Chemistry **24**(49): 12890-12901.

Combination therapies for tumors based on different therapeutic approaches should try to improve treatment efficacy, but also to reduce side-effects related to the exogenous stimulus and premature release. In the following study, we established and validated a pH/near-infrared (NIR)/glutathione (GSH)/-responsive multifunctional disulfide cross-linked Fe3 O4 @C nanocarriers (ss-Fe3 O4 @C NCs) with black phosphorus quantum dots (BPQDs) as a capping agent. BPQDs and carbon shell of Fe3 O4 @C nanoparticles (NPs) were used as a photothermal agents, while the inner empty nucleus that allows for a high drug payload served as an effective drug carrier. These magnetofluorescent BPQDs@DOX@ss-Fe3 O4 @C NPs were conjugated with a targeting aptamer (epidermal growth factor receptor: EGFR), denoted as BPQDs@DOX@ss-Fe3 O4 @C-EGFR NPs, for targeting dual modal magnetic resonance (MR)/fluorescence imaging. The synthetic NCs showed that drug release was dependent on pH, near-infrared (NIR), and intracellular GSH levels, with minimum systemic release in the blood and maximum drug release within the tumors. Also, the photothermal effect resulting from the Fe3 O4 @C NPs and BPQDs upon application to NIR light caused a rapid rise in local temperature, which accounted for the highest enhancement of cell cytotoxicity. Thus, a theranostic system consisting of BPQDs@DOX@ss-Fe3 O4 @C-EGFR NPs is shown to generate excellent advantages in combined chemotherapy/photothermal therapy (PTT) with minimal side effects.

Zhang, M., et al. (2018). "Detection of CD22 Expression in Living Cancer Cells by Semiconductor Quantum Dots." J Biomed Nanotechnol **14**(8): 1375-1383.

CD22 is an important drug target for the treatment of autoimmune diseases and B cell-derived malignancies. In this study, N-acetylneuraminic acid functionalized quantum dots nanoconjugate was synthesized and used for targeting and fluorescence

imaging of CD22 on living cells. The nanoprobe was prepared by conjugating N-acetylneuraminic acid (NANA) on the carboxyl groups modified CdSe/ZnS quantum dots (COOH-QDs) via NHS/EDC mediated esterification. The NANA-QDs nanoprobe showed excellent size distribution, very low cytotoxicity and super fluorescent properties for biological imaging applications. The specificity of NANA-QDs nanoparticles for CD22 on living cancer cells was validated by cellular uptake inhibition assays, colocalization of the immunofluorescence staining with both anti-CD22 antibody and NANA-QDs nanoparticles. Furthermore, CD22 mediated endocytosis of NANA-QDs nanoparticles was investigated by cellular internalization kinetics in Daudi cells at multiple time points. The newly developed NANA-QDs based assay was successfully used to determine the expression levels of CD22 on various cancer cells, which were highly consistent with the results determined by immunofluorescence staining assay and western blotting. All these findings demonstrated that NANA-QDs nanoparticles system was a practical fluorescent nanoprobe for bioimaging of CD22, which held great promise in a wide variety of biomedical applications of CD22 related studies.

Zhang, X., et al. (2014). "Low-toxic Ag2S quantum dots for photoelectrochemical detection glucose and cancer cells." Biosens Bioelectron **56**: 307-312.

A new photoelectrochemical (PEC) biosensor was developed using low-toxic Ag2S QDs as photoelectrochemically active species. Energy levels of Ag2S and Ag2Se QD were compared to explain their differences in the PEC performance. The preparation condition of Ag2S QD was optimized and its structure characterization was measured. Then the developed photoelectric active interface was used to detect glucose and MCF-7 cancer cell and showed the good sensitivity and specificity. Under optimal condition, detection limits of 3.2 x 10(-5)M for glucose and 98 cells/mL for MCF-7 cell were achieved. Thus, the prepared Ag2S QD could serve as an excellent and promising photoelectric active material in the PEC biosensor.

Zhang, Y., et al. (2012). "Magnetic beads-based electrochemiluminescence immunosensor for determination of cancer markers using quantum dot functionalized PtRu alloys as labels." Analyst **137**(9): 2176-2182.

A novel electrochemiluminescence (ECL) immunosensor for sensitive detection of human chorionic gonadotrophin antigen (HCG-Ag) was constructed using CdTe quantum dot functionalized nanoporous PtRu alloys (QDs@PtRu) as labels for signal amplification. In this paper, nanoporous PtRu alloy was employed as the carrier for immobilization of CdTe QDs and antibodies. Primary monoclonal antibody to alfa-HCG antigen (McAb(1)) was immobilized onto the surface of chitosan coated Fe(3)O(4) magnetic nanoparticles (Fe(3)O(4)/CS MNPs) by glutaraldehyde (GA) as coupling agent. Then McAb(1) could be easily separated and assembled on the surface of indium tin oxide glass (ITO) owing to their excellent magnetic properties with external magnetic forces holding the MNPs. Due to signal amplification from the high loading of CdTe QDs, 4.67-fold enhancements in ECL signal for HCG-Ag detection was achieved compared to the unamplified method (single QDs as labels). Under optimal conditions, a wide detection range (0.005~50 ng mL(-1)) and low detection limit (0.8 pg mL(-1)) were achieved through the sandwich-type immunosensor. The novel immunosensor showed high sensitivity and selectivity, excellent stability, and good reproducibility, and thus has great potential for clinical detection of HCG-Ag. In particular, this approach presents a novel class of combining bifunctional nanomaterials with preferable ECL properties and excellent magnetism, which suggests considerable potential in a wide range of applications for bioassays.

Zhang, Y., et al. (2013). "Self-assembly of folate onto polyethyleneimine-coated CdS/ZnS quantum dots for targeted turn-on fluorescence imaging of folate receptor overexpressed cancer cells." Anal Chem **85**(1): 228-234.

Folate receptor (FR) can be overexpressed by a number of epithelial-derived tumors, but minimally expressed in normal tissues. As folic acid (FA) is a high-affinity ligand to FR, and not produced endogenously, development of FA-conjugated probes for targeted imaging FR overexpressed cancer cells is of significance for assessing cancer therapeutics and for better understanding the expression profile of FR in cancer. Here we report a novel turn-on fluorescence probe for imaging FR overexpressed cancer cells. The probe was easily fabricated via electrostatic self-assembly of FA and polyethyleneimine-coated CdS/ZnS quantum dots (PEI-CdS/ZnS QDs). The primary fluorescence of PEI-CdS/ZnS QDs turned off first upon the electrostatic adsorption of FA onto PEI-CdS/ZnS QDs based on electron transfer to produce negligible fluorescence background. The presence of FR expressed on the surface of cancer cells then made FA desorb from PEI-CdS/ZnS QDs due to specific and high affinity of FA to FR. As a result, the primary fluorescence of PEI-CdS/ZnS QDs adhering to the cells turned on due to the inhibition of electron transfer. The most important merits of the developed probe are its simplicity and the effective avoidance of the false positive results due to the simple electrostatic self-assembly of FA onto the surface of PEI-CdS/ZnS QDs and the involved fluorescence "off-on" mechanism. The probe was

demonstrated to be sensitive and selective for targeted imaging of FR overexpressed cancer cells in turn-on mode.

Zhang, Y., et al. (2012). "Water induced protonation of amine-terminated micelles for direct syntheses of ZnO quantum dots and their cytotoxicity towards cancer." Nanoscale **4**(11): 3530-3535.

This work designs a new strategy for the direct synthesis of different zinc oxide (ZnO) nanostructures at low temperatures. Micelles of dodecylamine (DDA) assembled in an ethanol-water system have been explored as a template to direct the growth of the ZnO nanostructures. The key species for the formation of the ZnO nanostructures, OH(-), can be provided by the water-induced protonation of DDA. The pH of the reaction micro-environment can be regulated by changing the input amount of water and DDA. By controlling the reaction temperature and pH, various ZnO nanostructures, i.e. quantum dots with green or yellow-green emissions, have been prepared. The relationship of the optical properties and the synthetic conditions has been further discussed. This strategy realizes the convenient preparation of ZnO QDs, indicating the potential prospects in the nanotechnology field for their low-cost synthesis. Meanwhile, the cellular toxicity study of ZnO nanoparticles toward cancer cells, including leukemia K562 and K562/A02 cells as well as HepG2 cells, indicates a selective cytotoxic effect of ZnO QDs against a broad range of human cancer cell lines.

Zhang, Y. P., et al. (2012). "In vitro gastric cancer cell imaging using near-infrared quantum dot-conjugated CC49." Oncol Lett **4**(5): 996-1002.

In this experiment, we developed a bioprobe label for immunofluorescence using gastric tumor-specific quantum dots (QDs) to detect gastric tumor cells in vitro. The fluorescent probe, which is capable of specifically labeling gastric tumor cells, was constructed by taking advantage of the unique and superior properties of QDs. We grafted primary QDs onto the tumor-associated glycoprotein 72 (TAG-72) monoclonal antibody CC49 to produce CC49-QDs that specifically label tumor cells. Following a series of tests on the diameter and emission spectrum of CC49-QDs, they were employed in immunofluorescence analysis. Transmission electron microscopy and fluorescence spectrum analyses indicated that CC49-QDs had a 0.25 nm higher average diameter than the primary QDs, and that the grafted CC49 had no difference in optical properties compared to the primary QDs. In cell imaging, the cells labeled with CC49-QDs generated brighter fluorescence compared with the cells of the primary QD group. The results of immunofluorescence analysis demonstrated that antibody grafting reinforced the specific binding of QDs to tumor cells. This probe may also be further applied to live gastric cancer animal models to track lymphatic metastasis. In addition, it may potentially offer theoretical support for lymphadenectomy in the treatment of gastric cancer.

Zhao, M. X. and B. J. Zhu (2016). "The Research and Applications of Quantum Dots as Nano-Carriers for Targeted Drug Delivery and Cancer Therapy." Nanoscale Res Lett **11**(1): 207.

Quantum dots (QDs), nano-carriers for drugs, can help realize the targeting of drugs, and improve the bioavailability of drugs in biological fields. And, a QD nano-carrier system for drugs has the potential to realize early detection, monitoring, and localized treatments of specific disease sites. In addition, QD nano-carrier systems for drugs can improve stability of drugs, lengthen circulation time in vivo, enhance targeted absorption, and improve the distribution and metabolism process of drugs in organization. So, the development of QD nano-carriers for drugs has become a hotspot in the fields of nano-drug research in recent years. In this paper, we review the advantages and applications of the QD nano-carriers for drugs in biological fields.

Zhao, P., et al. (2021). "Biomimetic black phosphorus quantum dots-based photothermal therapy combined with anti-PD-L1 treatment inhibits recurrence and metastasis in triple-negative breast cancer." J Nanobiotechnology **19**(1): 181.

BACKGROUND: Triple-negative breast cancer (TNBC) is a highly aggressive malignant disease with a high rate of recurrence and metastasis, few effective treatment options and poor prognosis. Here, we designed and constructed a combined photothermal immunotherapy strategy based on cancer cell membrane-coated biomimetic black phosphorus quantum dots (BBPQDs) for tumor-targeted photothermal therapy and anti-PD-L1 mediated immunotherapy. RESULTS: BBPQDs have good photothermal conversion efficiency and can efficiently target tumor cells through homologous targeting and tumor homing. Under near infrared irradiation, we found that BBPQDs kill tumors directly through photothermal effects and induce dendritic cells maturation. In vivo studies have confirmed that the combined photothermal immunotherapy strategy displays a stronger antitumor activity than anti-PD-L1 monotherapy. In addition, BBPQDs-mediated photothermal therapy in combination with anti-PD-L1 treatment inhibit tumor recurrence and metastasis by reprograming the immunosuppressive tumor microenvironment into an immune-active microenvironment, and promoting the local and systemic antitumor immune response. We further found that the combined photothermal immunotherapy strategy can produce an immune

memory effect against tumor rechallenge. CONCLUSIONS: This study provides a novel therapeutic strategy for inhibiting the recurrence and metastasis of TNBC, with broad application prospects.

Zhao, T., et al. (2021). "A pH-activated charge convertible quantum dot as a novel nanocarrier for targeted protein delivery and real-time cancer cell imaging." Mater Sci Eng C Mater Biol Appl **118**: 111449.

The rapid developments of nanocarriers based on quantum dots (QDs) have been confirmed to show substantial promise for drug delivery and bioimaging. However, optimal QDs-based nanocarriers still need to have their controlled behavior in vitro and in vivo and decrease heavy metal-associated cytotoxicity. Herein, a pH-activated charge convertible QD-based nanocarrier was fabricated by capping multifunctional polypeptide ligands (mPEG-block-poly(ethylenediamine-dihydrolipoic acid-2,3-dimethylmaleic anhydride)-L-glutamate, PEG-P(ED-DLA-DMA)LG) onto the surface of core/multishell CdSe@ZnS/ZnS QD by means of a ligand exchange strategy, followed by uploading of cytochrome C (CC) (CC-loaded QD-PEG-P(ED-DLA-DMA)LG) via electrostatic interactions, in which QDs that were water-soluble and protein-loading were perfectly integrated. That is, the CC-loaded QD-PEG-P(ED-DLA-DMA)LG inherited excellent fluorescence properties from CdSe@ZnS/ZnS QD for real-time imaging, as well as tumor-microenvironment sensitivities from PEG-P(ED-DLA-DMA)LG for enhanced cellular uptake and CC release. Experimental results verified that the QD-PEG-P(ED-DLA-DMA)LG showed enhanced internalization, rapid endo/lysosomal escape, and supplied legible real-time imaging for lung carcinoma cells. Furthermore, pH-triggered charge-convertible ability enabled the QD-PEG-P(ED-DLA-DMA)LG-CC to effectively kill cancer cells better than did the control groups. Hence, constructing smart nanocomposites by facile ligand-exchange strategy is beneficial to QD-based nanocarrier for tumor-targeting cancer therapy.

Zheng, H., et al. (2010). "Detection of the cancer marker CD146 expression in melanoma cells with semiconductor quantum dot label." J Biomed Nanotechnol **6**(4): 303-311.

The use of highly specific and highly sensitive quantum dots immunofluorescent label is a promising approach for biomedical imaging in cancer cells. Human melanoma cell adhesion molecule CD146, overexpressed on the surface of melanoma cells, is an important target for melanoma diagnostics. We synthesized PEG-COOH capped highly fluorescent CdSe/ZnS QDs and conjugated them with streptavidin to prepare QD-SA label. Then, we used QD-SA to link with biotinylated goat anti-mouse IgG and mouse anti-human CD146 to label CD146 overexpressed on live and fixed cells by FACS and Confocal microscopy. Labeling of target cells was shown to have high brightness, photostability, and specificity. Advantages of QD conjugates over FITC conjugates are discussed. The results indicate that construction based on QD-SA label, biotinylated IgG and CD146 antibody can be successfully used for detection of melanoma cells for biomedical applications.

Zheng, H., et al. (2016). "Quantum dot-based immunofluorescent imaging and quantitative detection of TOP2A and prognostic value in triple-negative breast cancer." Int J Nanomedicine **11**: 5519-5529.

BACKGROUND: Topoisomerase 2 alpha (TOP2A) is a key enzyme in DNA replication and a target of various cytotoxic agents including anthracyclines. Previous studies evaluating the predictive and prognostic values of TOP2A in breast cancer are contradictory, likely secondary to the use of both different detection methods and different cutoff thresholds for positive status. Our own studies have previously confirmed the advantages of quantum dot-based nanotechnology for quantitative analysis of biomarkers relative to conventional immunohistochemistry (IHC). This study was designed to 1) assess the expression of TOP2A, 2) investigate the relationship between TOP2A expression and major clinical pathological parameters, and 3) evaluate the prognostic value of TOP2A by quantum dot-based immunofluorescent imaging and quantitative analytical system (QD-IIQAS) in triple-negative breast cancer (TNBC). PATIENTS AND METHODS: TOP2A expression in 145 TNBC specimens was detected using IHC and QD-IIQAS, and a comparative analysis of the two methods was conducted, including an exploration of the relationship between TOP2A expression and major clinical pathological parameters in TNBC. The prognostic value of TOP2A in TNBC was assessed. RESULTS: A similar antigen localization, a high correlation of staining rates (r=0.79), and a high agreement of measurements (kappa=0.763) of TOP2A expression in TNBC were found by QD-IIQAS and conventional IHC (cutoff: 45.0 and 0.45, respectively). TOP2A was significantly higher in larger tumors (P=0.002), higher grade tumors (P=0.005), and lymph node positive patients (P<0.001). The 5-year disease-free survival (5-DFS) of the high and low TOP2A subgroups was significantly different for both QD-IIQAS and IHC (P<0.001, log-rank test for both). TOP2A expression was an independent predictor of survival in TNBC (P=0.001). CONCLUSION: QD-IIQAS was an easy and accurate method for detecting and assessing TOP2A. The TOP2A expression was an independent prognostic indicator of 5-DFS in TNBC.

Our study provides a good foundation for future studies exploring the relationship between TOP2A expression and response to anthracyclines.

Zheng, H. M., et al. (2016). "Quantum dot-based in situ simultaneous molecular imaging and quantitative analysis of EGFR and collagen IV and identification of their prognostic value in triple-negative breast cancer." Tumour Biol **37**(2): 2509-2518.

Triple-negative breast cancer (TNBC) is a unique breast cancer subtype with high heterogeneity and poor prognosis. Currently, the treatment effect of TNBC has reached a bottleneck, rendering new breakthroughs difficult. Cancer invasion is not an entirely cell-autonomous process, requiring the cells to transmigrate across the surrounding extracellular matrix (ECM) barriers. Developing a new system that integrates key constituents in the tumor microenvironment with pivotal cancer cell molecules is essential for the in-depth investigation of the mechanism of invasion in TNBC. We describe a computer-aided algorithm developed using quantum dot (QD)-based multiplex molecular imaging of TNBC tissues. We performed in situ simultaneous imaging and quantitative detection of epidermal growth factor receptor (EGFR), expressed in the TNBC cell membrane, and collagen IV, the major ECM constituent; calculated the EGFR/collagen IV ratio; and investigated the prognostic value of the EGFR/collagen IV ratio in TNBC. We simultaneously imaged and quantitatively detected EGFR and collagen IV in the TNBC samples. In all patients, quantitative determination showed a statistically significant negative correlation between EGFR and collagen IV. The 5-year disease-free survival (5-DFS) of the high and low EGFR/collagen IV ratio subgroups was significantly different. The EGFR/collagen IV ratio was predictive and was an independent prognostic indicator in TNBC. Compared with EGFR expression, the EGFR/collagen IV ratio had a greater prognostic value for 5-DFS. Our findings open up a new avenue for predicting the clinical outcome in TNBC from the perspective of integrating molecules expressed in both cancer cells and the ECM.

Zhong, H., et al. (2011). "High-intensity fluorescence imaging and sensitive electrochemical detection of cancer cells by using an extracellular supramolecular reticular DNA-quantum dot sheath." Chemistry **17**(30): 8388-8394.

Acting as a cage-type cellular probe, an extracellular supramolecular reticular DNA-quantum dot (QD) sheath has been developed for high-intensity fluorescence microscopy imaging and the sensitive electrochemical detection of Ramos cells. The extracellular supramolecular reticular DNA-QD sheath is constructed from layer-by-layer self-assembly of DNA-CdTe QD probes and DNA nanowire frameworks functionalized with a Ramos cell-binding aptamer. The DNA-QD sheath forms specifically and quickly on the surface of Ramos cells at physiological temperature, and the assembly of large numbers of DNA-CdTe QD probes on the surface of Ramos cells produces exceedingly high fluorescence intensity. Using the extracellular supramolecular reticular DNA-QD sheath as the cellular probe, Ramos cells can be clearly observed and easily distinguished from a mixture of multiple cancer cells by fluorescence microscopy imaging. Using the new cage-type cellular probe, a sensitive sandwich-type electrochemical strategy has also been developed to achieve accurate quantitative analysis of Ramos cells. Under the optimized conditions, Ramos cells can be detected quantitatively in a range from 10 to 1000 cells with a detection limit of 10 cells. This strategy presents a promising platform for highly sensitive and convenient evaluation of cancer cell levels.

Zhou, Y., et al. (2010). "Imaging and inhibition of multi-drug resistance in cancer cells via specific association with negatively charged CdTe quantum dots." Biomaterials **31**(18): 4958-4963.

Photoluminescent semiconductor quantum dots (QDs) have received significant attention in biological and biomedical fields because of their attractive properties. In this contribution, we have explored and evaluated the utilization of water-soluble nanocrystal CdTe quantum dots (QDs) capped with negatively charged 3-mercapitalpropionic acid (MPA)-QDs to enhance the drug uptake into the target cancer cells and the efficiency of the biomarker and cancer treatments, by using the cytotoxicity evaluation, total internal reflection fluorescence microscopy, electrochemistry and UV-Vis absorption spectroscopy. Our results illustrate that the MPA-CdTe QDs could effectively facilitate the interaction of anticancer agent daunorubicin (DNR) with leukemia cells and the efficiency of biolabeling in cancer cells. Therefore, the present study affords a new potential method for simultaneous cellular inhibition and imaging of cancer cells.

Zhu, Y. Y., et al. (2018). "The prognostic value of quantitative analysis of CCL5 and collagen IV in luminal B (HER2-) subtype breast cancer by quantum-dot-based molecular imaging." Int J Nanomedicine **13**: 3795-3803.

OBJECTIVE: Breast cancer is the most common malignancy and one of the main causes of death in women. Luminal B (HER2-) breast cancer subtype has been proposed since the 2011 St Gallon consensus. The hormone receptor status in this type of breast cancer is positive; thus, endocrine therapy was

performed in all cases, but the treatment was not satisfactory, and a significant number of cases received very little benefit from chemotherapy. Furthermore, there is no effective treatment target for this subtype. Luminal B (HER2-) breast cancer subtype has been proposed since the 2011 St Gallon consensus. Therefore, the study of the key molecules in the microenvironment of breast cancer can help to reveal the biological characteristics. PATIENTS AND METHODS: Luminal B (HER2-) breast cancer is a subtype with higher heterogeneity and poorer prognosis than luminal A. It is known that the development of cancer cells is an active process, and this process needs microenvironment cytokines, including chemokine (C-C motif) ligand 5 (CCL5) and collagen IV. Therefore, CCL5 and collagen IV were imaged and detected by quantum dot, and the CCL5/collagen IV ratio was calculated to investigate the prognostic value of the CCL5/collagen IV ratio in luminal B (HER2-). RESULTS: Quantitative determination showed a statistically significant negative correlation between CCL5 and collagen IV. The 5-year disease-free survival (5-DFS) of the high and low CCL5/collagen IV ratio subgroups was significantly different. The CCL5/collagen IV ratio had a greater prognostic value for 5-DFS. The CCL5/collagen IV ratio was an independent prognostic indicator. CONCLUSION: Our findings revealed the effective integration of tumor CCL5 and collagen IV, and a new method for predicting the prognosis of luminal B (HER2-) has been developed.

Zu, R., et al. (2020). "Peptide-enabled receptor-binding-quantum dots for enhanced detection and migration inhibition of cancer cells." J Biomater Sci Polym Ed **31**(12): 1604-1621.

We report the efforts to construct active targeting quantum dots using receptor-binding peptide for enhanced detection and migration inhibition of cancer cells. Peptide E5 has specific binding with chemokine receptor 4 (CXCR4), which is a transmembrane G-coupled receptor involved in the metastasis of various types of cancers. E5 was introduced to the surface of CdSe/ZnS quantum dots via biotin-streptavidin interactions. The constructed CXCR4-targeting quantum dots (E5@QDs) was observed to display improved detection sensitivity and significantly enhanced binding affinity for CXCR4 over-expressed cancer cells, and the ability to inhibit cancer cells migration induced by CXCL12.

The following introduces recent reports as references in the related studies.

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12/15/2022