



## Cancer Biology Research Literatures

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**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.

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**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. This article introduces recent research reports as references in the related studies.

The following introduces recent reports as references in the related studies.

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 15µg/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.

Abdelhameed, M., et al. (2018). "Tuning the Optical Properties of Silicon Quantum Dots via Surface Functionalization with Conjugated Aromatic Fluorophores." *Sci Rep* **8**(1): 3050.

Silicon Quantum Dots (SQDs) have recently attracted great interest due to their excellent optical properties, low cytotoxicity, and ease of surface modification. The size of SQDs and type of ligand on their surface has a great influence on their optical properties which is still poorly understood. Here we report the synthesis and spectroscopic studies of three families of unreported SQDs functionalized by covalently linking to the aromatic fluorophores, 9-vinylphenanthrene, 1-vinylpyrene, and 3-vinylperylene. The results showed that the prepared functionalized

SQDs had a highly-controlled diameter by HR-TEM, ranging from 1.7-2.1 nm. The photophysical measurements of the assemblies provided clear evidence for efficient energy transfer from the fluorophore to the SQD core. Frster energy transfer is the likely mechanism in these assemblies. As a result of the photogenerated energy transfer process, the emission color of the SQD core could be efficiently tuned and its emission quantum efficiency enhanced. To demonstrate the potential application of the synthesized SQDs for bioimaging of cancer cells, the water-soluble perylene- and pyrene-capped SQDs were examined for fluorescent imaging of HeLa cells. The SQDs were shown to be of low cytotoxicity.

Abeyasinghe, N., et al. (2016). "Enhanced Emission from Single Isolated Gold Quantum Dots Investigated Using Two-Photon-Excited Fluorescence Near-Field Scanning Optical Microscopy." *J Am Chem Soc* **138**(50): 16299-16307.

New approaches in molecular nanoscopy are greatly desired for interrogation of biological, organic, and inorganic objects with sizes below the diffraction limit. Our current work investigates emergent monolayer-protected gold quantum dots (nanoclusters, NCs) composed of 25 Au atoms by utilizing two-photon-excited fluorescence (TPEF) near-field scanning optical microscopy (NSOM) at single NC concentrations. Here, we demonstrate an approach to synthesize and isolate single NCs on solid glass substrates. Subsequent investigation of the NCs using TPEF NSOM reveals that, even when they are separated by distances of several tens of nanometers, we can excite and interrogate single NCs individually. Interestingly, we observe an enhanced two-photon absorption (TPA) cross section for single Au<sub>25</sub> NCs that can be attributed to few-atom local field effects and to local field-induced microscopic cascading, indicating their potential for use in ultrasensitive sensing, disease diagnostics, cancer cell therapy, and molecular computers. Finally, we report room-temperature aperture-based TPEF NSOM imaging of these NCs for the first time at 30 nm point resolution, which is a approximately 5-fold improvement compared to the previous best result for the same technique. This report unveils the unique combination of an unusually large TPA cross section and the high photostability of Au NCs to (non-destructively) investigate stable isolated single NCs using TPEF NSOM. This is the first reported optical study of monolayer-protected single quantum clusters, opening some very promising opportunities in spectroscopy of nanosized objects, bioimaging, ultrasensitive sensing, molecular computers, and high-density data storage.

Antaris, A. L., et al. (2017). "A high quantum yield molecule-protein complex fluorophore for near-infrared II imaging." *Nat Commun* **8**: 15269.

Fluorescence imaging in the second near-infrared window (NIR-II) allows visualization of deep anatomical features with an unprecedented degree of clarity. NIR-II fluorophores draw from a broad spectrum of materials spanning semiconducting nanomaterials to organic molecular dyes, yet unfortunately all water-soluble organic molecules with >1,000 nm emission suffer from low quantum yields that have limited temporal resolution and penetration depth. Here, we report tailoring the supramolecular assemblies of protein complexes with a sulfonated NIR-II organic dye (CH-4T) to produce a brilliant 110-fold increase in fluorescence, resulting in the highest quantum yield molecular fluorophore thus far. The bright molecular complex allowed for the fastest video-rate imaging in the second NIR window with approximately 50-fold reduced exposure times at a fast 50 frames-per-second (FPS) capable of resolving mouse cardiac cycles. In addition, we demonstrate that the NIR-II molecular complexes are superior to clinically approved ICG for lymph node imaging deep within the mouse body.

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.

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.

Bali Prasad, B., et al. (2017). "Synthesis of novel monomeric graphene quantum dots and corresponding nanocomposite with molecularly imprinted polymer for electrochemical detection of an anticancerous ifosfamide drug." *Biosens Bioelectron* **94**: 1-9.

This paper reports a typical synthesis of a nanocomposite of functionalized graphene quantum dots and imprinted polymer at the surface of screen-printed carbon electrode using N-acryloyl-4-aminobenzamide, as a functional monomer, and an anticancerous drug, ifosfamide, as a print molecule (test analyte). Herein, graphene quantum dots in nanocomposite practically induced the electrocatalytic activity by lowering the oxidation overpotential of test analyte and thereby amplifying electronic transmission, without any interfacial barrier in between the film and the electrode surface. The differential pulse anodic stripping signal at functionalized graphene quantum dots based imprinted sensor was realized to be about 3- and 7-fold higher as compared to the traditionally made imprinted polymers prepared in the presence and the absence of graphene quantum dots (un-functionalized), respectively. This may be attributed to a pertinent synergism in between the positively charged functionalized graphene quantum dots in the film and the target analyte toward the enhancement of electroconductivity of the film and thereby the electrode

kinetics. In fact, the covalent attachment of graphene quantum dots with N-acryloyl-4-aminobenzamide molecules might exert an extended conjugation at their interface facilitating electro conducting to render the channelized pathways for the electron transport. The proposed sensor is practically applicable to the ultratrace evaluation of ifosfamide in real (biological/pharmaceutical) samples with detection limit as low as 0.11ngmL(-1) (S/N=3), without any matrix effect, cross-reactivity, and false-positives.

Bao, Y. W., et al. (2018). "Hyperthermia-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.

Biava, P. M., et al. (2017). "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*.

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 re-differentiation often signifies the phenotypic reversion back to health and non-proliferation. 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.

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-Fluorouracil (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-Fluorouracil loaded Mn:ZnS quantum dots towards 4T1 cell line proliferation in mice based on the histological analysis.

Borghesi, Y. S., et al. (2018). "A novel BRCA1 gene deletion detection in human breast carcinoma MCF-7 cells through FRET between quantum dots and silver nanoclusters." *J Pharm Biomed Anal* **152**: 81-88.

BRCA1 (breast cancer 1) genomic deletions are the most important founder mutations in breast cancer patients and can be passed to you from your mother or father. Herein, we report a silver nanoclusters-based (AgNCs-based) fluorescence resonance energy transfer (FRET) method for detection of BRCA1 gene deletion. The method relies on the specific hybridization of DNA-AgNCs fluorescent probe to deleted genes and interaction between double stranded DNA-AgNCs and QD, and the signal amplification through energy transfer from fluorescent AgNCs to QDs during FRET. Such fabricated QDs/DNA-AgNCs interaction might be beneficial for the nanomaterials based biosensing methods Under best possible conditions a linear correlation was established between the fluorescence intensity and the concentration of deletion sequence in the range of  $5.0 \times 10^{-13}$ - $1.0 \times 10^{-9}$ M with a detection limit of  $1.2 \times 10^{-13}$ M. Using this method, we could effectively determine gene deletions by using the nonamplified genomic DNAs that were extracted from the MCF-7 as a breast cancer cell line.

Boriachek, K., et al. (2017). "Quantum dot-based sensitive detection of disease specific exosome in serum." *Analyst* **142**(12): 2211-2219.

Tumor-derived exosomes have emerged as promising cancer biomarkers due to their unique composition and functions. Herein, we report a stripping voltammetric immunoassay for the electrochemical detection of disease-specific exosomes using quantum dots as signal amplifiers. The assay involves three subsequent steps where bulk exosome populations are initially magnetically captured on magnetic beads by a generic tetraspanin antibody (e.g., CD9 or CD63) followed by the identification of disease-specific exosomes using cancer-related. Here, we used CdSe quantum dot (CdSeQD) functionalised-biotinylated HER-2 and FAM134B antibodies as breast and colon cancer markers. After magnetic washing and purification steps, acid dissolution of CdSeQDs and subsequent anodic stripping voltammetric quantification of Cd(2+) were carried out at the bare glassy carbon working electrode. This method enabled sensitive detection of 100 exosomes per  $\mu$ L with a relative standard deviation (%RSD) of <5.5% in cancer cell lines and a small cohort of serum samples (n = 9) collected from patients with colorectal adenocarcinoma. We believe that our approach could potentially represent an effective bioassay for the quantification of disease-specific exosomes in clinical samples.

Brunetti, J., et al. (2018). "Near-infrared quantum dots labelled with a tumor selective tetrabrached peptide for in vivo imaging." *J Nanobiotechnology* **16**(1): 21.

**BACKGROUND:** Near-infrared quantum dots (NIR QDs) are a new class of fluorescent labels with excellent bioimaging features, such as high fluorescence intensity, good fluorescence stability, sufficient electron density, and strong tissue-penetrating ability. For all such features, NIR QDs have great potential for early cancer diagnosis, in vivo tumor imaging and high resolution electron microscopy studies on cancer cells. **RESULTS:** In the present study we constructed NIR QDs functionalized with the NT4 cancer-selective tetrabrached peptides (NT4-QDs). We observed specific uptake of NT4-QDs in human cancer cells in in vitro experiments and a much higher selective accumulation and retention of targeted QDs at the tumor site, compared to not targeted QDs, in a colon cancer mouse model. **CONCLUSIONS:** NIR QDs labelled with the tetrabrached NT4 peptide have very promising performance for selective addressing of tumor cells in vitro and in vivo, proving rising features of NT4-QDs as theranostics.

Cadkova, M., et al. (2018). "Electrochemical quantum dots-based magneto-immunoassay for detection of HE4 protein on metal film-modified screen-printed carbon electrodes." *Talanta* **182**: 111-115.

A novel enzyme-free electrochemical immunosensor was developed for highly sensitive detection and quantification of human epididymis protein 4 (HE4) in human serum. For the first time, core/shell CdSe/ZnS quantum dots were conjugated with anti-HE4 IgG antibodies for subsequent sandwich-type immunosensing with superparamagnetic microparticles functionalized with anti-HE4 IgG antibodies, which allow rapid and efficient HE4 capture from the sample. Electrochemical detection of anti-HE4 IgG - HE4 - anti-HE4 IgG(CdSe/ZnS) immunocomplex was performed by recording the current response of Cd(II) ions, released from dissolved quantum dots at screen-printed carbon electrode (SPCE), modified with mercury or bismuth film. The linear range of the detection was from 20pM to 40nM with limit of detection of 12pM using three times the standard deviation of blank criterion at mercury-film SPCE and from 100pM to 2nM with limit of detection of 89pM at bismuth-film SPCE. Proposed electrochemical immunosensor meets the requirements for fast and sensitive quantification of HE4 biomarker in early stage of ovarian cancer and due to the proper sensitivity and specificity presents a promising alternative to enzyme-based probes used routinely in clinical diagnostics.

Cao, Y., et al. (2017). "Aptamer-Conjugated Graphene Quantum Dots/Porphyrim 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.

Chan, M. H., et al. (2016). "Near-Infrared Light-Mediated Photodynamic Therapy Nanoplatform by the Electrostatic Assembly of Upconversion Nanoparticles with Graphitic Carbon Nitride Quantum Dots." *Inorg Chem* **55**(20): 10267-10277.

Photodynamic therapy (PDT) is a promising antitumor treatment that is based on photosensitizers. This therapy kills cancer cells by generating reactive oxygen species (ROS) after irradiation with specific laser wavelengths. Being a potential photosensitizer, graphitic carbon nitride (g-C<sub>3</sub>N<sub>4</sub>) quantum dots (QDs) are noncytotoxic. Although the use of g-C<sub>3</sub>N<sub>4</sub> QDs is challenged by the limited tissue penetration of UV light, g-C<sub>3</sub>N<sub>4</sub> QDs display excellent ultraviolet (UV) light-triggered cytotoxicity. The g-C<sub>3</sub>N<sub>4</sub> QDs were synthesized using a solid-phase hydrothermal method. The well-distributed hydrophilic g-C<sub>3</sub>N<sub>4</sub> can be combined with NaYF<sub>4</sub>:Yb(3+)/Tm(3+) upconversion nanoparticles via the positive ligand poly(L-lysine) to produce the final nanocomposite, NaYF<sub>4</sub>:Yb/Tm-PLL@g-C<sub>3</sub>N<sub>4</sub>. Upconversion nanoparticles can transfer IR light into UV light and promote g-C<sub>3</sub>N<sub>4</sub> to release blue-to-green visible light to generate different images. Moreover, g-C<sub>3</sub>N<sub>4</sub> is a promising

photosensitizer in PDT because g-C<sub>3</sub>N<sub>4</sub> can transfer oxygen into toxic ROS. The singlet oxygen formed by g-C<sub>3</sub>N<sub>4</sub> displays great potential for use in the treatment of cancer.

Chen, H., et al. (2017). "Quantum dot light emitting devices for photomedical applications." *J Soc Inf Disp* **25**(3): 177-184.

While OLEDs have struggled to find a niche lighting application that can fully take advantage of their unique form factors as thin, flexible, lightweight and uniformly large-area luminaire, photomedical researchers have been in search of low-cost, effective illumination devices with such form factors that could facilitate widespread clinical applications of photodynamic therapy (PDT) or photobiomodulation (PBM). Although existing OLEDs with either fluorescent or phosphorescent emitters cannot achieve the required high power density at the right wavelength windows for photomedicine, the recently developed ultrabright and efficient deep red quantum dot light emitting devices (QLEDs) can nicely fit into this niche. Here, we report for the first time the in-vitro study to demonstrate that this QLED-based photomedical approach could increase cell metabolism over control systems for PBM and kill cancerous cells efficiently for PDT. The perspective of developing wavelength-specific, flexible QLEDs for two critical photomedical fields (wound repair and cancer treatment) will be presented with their potential impacts summarized. The work promises to generate flexible QLED-based light sources that could enable the widespread use and clinical acceptance of photomedical strategies including PDT and PBM.

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, M. L., et al. (2017). "Synthesis of permeable yolk-shell structured gadolinium-doped quantum dots as a potential nanoscale multimodal-visible delivery system." *Talanta* **175**: 280-288.

Developing a nanoscale drug delivery system with magnetic resonance imaging (MRI)/fluorescence imaging (FL) visibility to optimize the delivery efficiency and therapeutic efficacy under image guidance has attracted great attentions in the area of nanomedicine. Herein, a novel permeable yolk-shell structured gadolinium-doped quantum dots nanocomposite was synthesized as a theranostic nanocarrier via an indirectly doping method. The as-prepared permeable nanoparticles with tunable color fluorescent emission, paramagnetic and accessible mesoporous channels could be developed as a novel nanomedical platform for integrated multimodal diagnosis and therapy. The hydrophilic nanocomposites exhibited tunable fluorescence as well as high longitudinal relaxivity ( $r_1 = 17.32\text{mM}^{-1}\text{s}^{-1}$ ) in water with good colloidal stability. In vivo animal experiments further verified CSSP could achieve FL/MRI dual modality imaging. The widely used antineoplastic anthracycline drug doxorubicin (DOX) was absorbed into the permeable nanospheres with 95.3% loading efficiency and released in a pH-sensitive pattern. In vitro cancer cell cytotoxicity tests verified that the DOX-loaded nanocomposites had enhanced cytotoxicity compared with free DOX at the same concentration. The as-prepared nanocomposites present great potential as MRI/FL-visible nanoscale drug carrier to realize imaging-guided personalized therapy.

Chen, X., et al. (2018). "Highly cysteine-selective fluorescent nanoprobe based on ultrabright and directly synthesized carbon quantum dots." *Anal Bioanal Chem.*

Strongly green fluorescent carbon dots (CQDs) have been directly synthesized from 2,4-diaminophenylhydrazine and 2-hydroxy-5-methylisophthalaldehyde through a facile solvothermal method. The novel CQDs exhibit high fluorescence quantum yield and excellent water solubility due to the abundant amino and hydroxy groups on their surface. The use of the as-prepared CQDs combined with Cu(2+) constructed a "turn-on" switch cysteine-responsive nanoprobe. In the CQDs-Cu(2+) assemblies, the binding of Cu(2+) to CQDs results in the fluorescence quenching of CQDs by electron transfer mechanism, while the addition of cysteine leads to the fluorescence recovery because of the competitive binding between cysteine and CQDs to Cu(2+). The nanoprobe showed high sensitivity to cysteine with the detection limit of 2.6 nmol L<sup>-1</sup>. The selectivity investigation results demonstrated that the Cu(2+)-integrated nanoparticles were highly selective toward cysteine over the other amino acids and biologically related metal ions. The proposed nanoprobe was then employed for detecting the recovery of cysteine in rabbit serum and plasma samples and imaging the cysteine in cancer cells, and the recovery was found to be 98.2-104.0%. This "synthesis-modification integration" strategy for the fabrication of CQDs may offer a new sight for the preparation of multifunctional nanostructures and broadening the application of CQDs in bioimaging. Graphical abstract Fluorescent carbon dots (CQDs) were directly synthesized from 2,4-diaminophenylhydrazine and 2-hydroxy-5-methylisophthalaldehyde. CQDs exhibit high fluorescence quantum yield and excellent water solubility due to the abundant amino and hydroxy groups on their surface. The use of CQDs combined with Cu(2+) constructed a cysteine-responsive nanoprobe, which showed high sensitivity to cysteine with the detection limit of 2.6 nM.

Chen, X., et al. (2018). "Ultrasensitive detection of EGFR gene based on surface plasmon resonance enhanced electrochemiluminescence of CuZnInS quantum dots." *Anal Chim Acta* **1009**: 73-80.

In our work, a novel DNA electrochemiluminescence (ECL) sensor based on CuZnInS quantum dots (QDs) and gold-nanoparticles (Au NPs) is developed for highly sensitive detection of epidermal growth factor receptor (EGFR) Gene, which has a close relation with the lung cancer. The CuZnInS QDs work as a novel kind of ECL luminophore, whose defect state emission is suitable for ECL sensing. To enhance the sensitivity of the sensing system, Au NPs

are utilized creatively to strengthen the ECL intensity of CuZnInS QDS according to the surface plasmon resonance (SPR) effect. An ultrasensitive and universal detecting platform is built based on the SPR effect between Au NPs and CuZnInS QDS. The effect of the capped stabilizer on the ECL signal of QDs is firstly investigated. Three different stabilizers are used to cap the CuZnInS QDs, including mercaptopropionic acid (MPA), l-glutathione (GSH) and cysteamine (CA). MPA capped CuZnInS QDs possess the strongest ECL intensity among the three kinds of the CuZnInS QDs. Under the optimum conditions, a good linear relationship between ECL intensity and the concentration of target DNA is obtained in the range from 0.05nmolL(-1) to 1nmolL(-1). The detection limit is 0.0043nmolL(-1). The proposed DNA sensor has been employed for the determination of target DNA EGFR in human serum samples with satisfactory results.

Chen, Y., et al. (2018). "A Ligand System for the Flexible Functionalization of Quantum Dots via Click Chemistry." *Angew Chem Int Ed Engl*.

We present a novel ligand, 5-norbornene-2-nonanoic acid, which can be directly added during established quantum dot (QD) syntheses in organic solvents to generate "clickable" QDs at a few hundred nmol scale. This ligand has a carboxyl group at one terminus to bind to the surface of QDs and a norbornene group at the opposite end that enables straightforward phase transfer of QDs into aqueous solutions via efficient norbornene/tetrazine click chemistry. Our ligand system removes the traditional ligand-exchange step and can produce water-soluble QDs with a high quantum yield and a small hydrodynamic diameter of approximately 12 nm at an order of magnitude higher scale than previous methods. We demonstrate the effectiveness of our approach by incubating azido-functionalized CdSe/CdS QDs with 4T1 cancer cells that are metabolically labeled with a dibenzocyclooctyne-bearing unnatural sugar. The QDs exhibit high targeting efficiency and minimal nonspecific binding.

Chen, Z., et al. (2017). "Simultaneous quantitation of cytokeratin-19 fragment and carcinoembryonic antigen in human serum via quantum dot-doped nanoparticles." *Biosens Bioelectron* **91**: 60-65.

A novel quantum dot-doped polystyrene nanoparticles-based lateral flow test strips (QPs-LFTS) system was developed to simultaneously detect a cytokeratin-19 fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA) in human serum to aid the diagnosis and prognosis of lung cancer. Quantum dot-doped carboxylate-functionalized polystyrene nanoparticles (QPs) were prepared and

introduced as fluorescent reporters in QPs-LFTS. The detection was based on a sandwich immunoassay and performed on lateral flow test strips, with an assay time of 15min. The strips were read by a fluorescence strip reader to obtain the fluorescence peak heights of the test lines (HT) and the control line (HC). The ratio of HT/HC was used for quantitation. The QPs showed excellent photoproperties and good performance. Under optimal conditions, the QPs-LFTS system exhibited a wide linear range for CYFRA 21-1 (1.3-480ng/mL) and CEA (2.8-680ng/mL). The detection limits for CYFRA 21-1 and CEA were 0.16 and 0.35ng/mL, respectively. The recovery and reproducibility of the method were satisfactory. Furthermore, excellent correlations ( $n = 120$ ,  $R(2) = 0.9862$ ,  $P < 0.0001$  for CYFRA 21-1;  $n = 70$ ,  $R(2) = 0.9509$ ,  $P < 0.0001$  for CEA) were obtained between the QPs-LFTS and commercially available chemiluminescence immunoassay kits in clinical serum testing. The results indicate that this developed test system is highly efficient and is expected to be useful for early screening and prognosis evaluation for lung cancer patients.

Chen, Z. and M. Lu (2017). "Novel electrochemical immunoassay for human IgG1 using metal sulfide quantum dot-doped bovine serum albumin microspheres on antibody-functionalized magnetic beads." *Anal Chim Acta* **979**: 24-30.

A new magneto-controlled electrochemical immunosensing system was developed for the sensitive detection of low-abundance protein (IgG1 used in this case) with a sandwich-type assay format on monoclonal mouse anti-human Fab-specific IgG1-functionalized magnetic bead. Metal sulfide (CdS) quantum dot-doped bovine serum albumin (QD-BSA) was synthesized and functionalized with monoclonal Fc-specific anti-human antibody. In the presence of IgG1, the immobilized antibody on magnetic bead was selective to capture the Fab region of the analyte, followed to be sandwiched by the conjugated antibody onto QD-BSA. The subsequent anodic stripping voltammetric analysis of cadmium ion, released by acid from quantum dot, was conducted at an in situ prepared mercury film electrode. Under optimal conditions, the voltammetric current increased with the increasing of target IgG1 within a dynamic working range from 10 pg mL(-1) to 100 ng mL(-1). The limit of detection of this immunosensor was evaluated to 3.4 pg mL(-1) at 3sblank criterion. The precision, selectivity and method accuracy were acceptable. Analysis of human serum samples revealed good accordance with the results obtained by commercial enzyme-linked immunosorbent assay method. Importantly, this concept offers promise for cost-effective analysis of



low-abundance cancer biomarkers without the need of natural enzymes.

Chiu, S. H., et al. (2016). "Rapid fabrication of carbon quantum dots as multifunctional nanovehicles for dual-modal targeted imaging and chemotherapy." *Acta Biomater* **46**: 151-164.

Herein, we synthesized an S, N, and Gd tri-element doped magnetofluorescent carbon quantum dots (GdNS@CQDs) within 10min by using a one-pot microwave method. Our results showed that these magnetofluorescent GdNS@CQDs have excellent fluorescent and magnetic properties. Moreover, GdNS@CQDs exhibited high stability at physiological conditions and ionic strength. These magnetofluorescent GdNS@CQDs were conjugated with a folic acid, denoted as FA-GdNS@CQDs, for targeting dual modal fluorescence/magnetic resonance (MR) imaging. The in vitro and in vivo studies confirmed the high biocompatibility and low toxicity of FA-GdNS@CQDs. FA-GdNS@CQDs enhanced the MR response as compared to that for commercial Gd-DTPA. The targeting capabilities of FA-GdNS@CQDs were confirmed in HeLa and HepG2 cells using in vitro fluorescence and MR dual modality imaging. Additionally, an anticancer drug, doxorubicin, was incorporated into the FA-GdNS@CQDs forming FA-GdNS@CQDs-DOX, which enables targeted drug delivery. Importantly, the prepared FA-GdNS@CQDs-DOX showed a high quantity of doxorubicin loading capacity (about 80%) and pH-sensitive drug release. The uptake into cancer cells and the intracellular location of the FA-GdNS@CQDs were observed by confocal laser scanning microscopy. We also successfully demonstrated in vivo fluorescence bio imaging of the FA-GdNS@CQDs, using zebrafish as an animal model. STATEMENT OF SIGNIFICANCE: In this manuscript, we reported a facial, rapid, and environmental friendly method to fabricate hetero atoms including gadolinium, nitrogen, and sulfur doped multi-functional magnetofluorescent carbon quantum dots (GdNS@CQDs) nanocomposite. These multifunctional GdNS@CQDs were conjugated with a folic acid for targeting dual modal fluorescence/magnetic resonance imaging. Additionally, an anticancer drug, doxorubicin, was incorporated into the nanocomposite forming FA-GdNS@CQDs-DOX, which enables targeted drug delivery. We have developed GdNS@CQDs with integrated functions for simultaneous in vitro cell imaging, targeting, and pH-sensitive controlled drug release in HeLa cells. Furthermore, we successfully demonstrated the use of this material for in vivo fluorescence imaging, using zebrafish as an animal model.

Chua, E. G., et al. (2017). "Quantum changes in *Helicobacter pylori* gene expression accompany host-adaptation." *DNA Res* **24**(1): 37-49.

*Helicobacter pylori* is a highly successful gastric pathogen. High genomic plasticity allows its adaptation to changing host environments. Complete genomes of *H. pylori* clinical isolate UM032 and its mice-adapted serial derivatives 298 and 299, generated using both PacBio RS and Illumina MiSeq sequencing technologies, were compared to identify novel elements responsible for host-adaptation. The acquisition of a jhp0562-like allele, which encodes for a galactosyltransferase, was identified in the mice-adapted strains. Our analysis implies a new beta-1,4-galactosyltransferase role for this enzyme, essential for Ley antigen expression. Intragenomic recombination between babA and babB genes was also observed. Further, we expanded on the list of candidate genes whose expression patterns have been mediated by upstream homopolymer-length alterations to facilitate host adaptation. Importantly, greater than four-fold reduction of mRNA levels was demonstrated in five genes. Among the down-regulated genes, three encode for outer membrane proteins, including BabA, BabB and HopD. As expected, a substantial reduction in BabA protein abundance was detected in mice-adapted strains 298 and 299 via Western analysis. Our results suggest that the expression of Ley antigen and reduced outer membrane protein expressions may facilitate *H. pylori* colonisation of mouse gastric epithelium.

Cunha, C. R. A., et al. (2018). "Quantum dot-Cramoll lectin as novel conjugates to glycobiology." *J Photochem Photobiol B* **178**: 85-91.

The optical properties of quantum dots (QDs) make them useful tools for biology, especially when combined with biomolecules such as lectins. QDs conjugated to lectins can be used as nanoprobe for carbohydrate expression analysis, which can provide valuable information about glycosylation changes related to cancer and pathogenicity of microorganisms, for example. In this study, we evaluated the best strategy to conjugate Cramoll lectin to QDs and used the fluorescent labeling of *Candida albicans* cells as a proof-of-concept. Cramoll is a mannose/glucose-binding lectin with unique biological properties such as immunomodulatory, antiparasitic, and antitumor activities. We probed covalent coupling and adsorption as conjugation strategies at different pH values. QDs conjugated to Cramoll at pH7.0 showed the best labeling efficiency in the fluorescence microscopy analysis. Moreover, QD-Cramoll conjugates remained brightly fluorescent and preserved identical biological activity according to hemagglutination assays. Flow cytometry revealed that approximately 17% of *C. albicans* cells were labeled after incubation with

covalent conjugates, while approximately 92% of cells were labeled by adsorption conjugates (both at pH7.0). Inhibition assays confirmed QD-Cramoll specificity, which reduced the labeling to at most 3%. Therefore, the conjugates obtained by adsorption (pH7.0) proved to be promising and versatile fluorescent tools for glycobiology.

Cunha, C. R. A., et al. (2018). "Biomedical applications of glyconanoparticles based on quantum dots." *Biochim Biophys Acta* **1862**(3): 427-439.

**BACKGROUND:** Quantum dots (QDs) are outstanding nanomaterials of great interest to life sciences. Their conjugation versatility added to unique optical properties, highlight these nanocrystals as very promising fluorescent probes. Among uncountable new nanosystems, in the last years, QDs conjugated to glycans or lectins have aroused a growing attention and their application as a tool to study biological and functional properties has increased. **SCOPE OF REVIEW:** This review describes the strategies, reported in the literature, to conjugate QDs to lectins or carbohydrates, providing valuable information for the elaboration, improvement, and application of these nanoconjugates. It also presents the main applications of these nanosystems in glycobiology, such as their potential to study microorganisms, the development of diseases such as cancer, as well as to develop biosensors. **MAJOR CONCLUSIONS:** The development of glyconanoparticles based on QDs emerged in the last decade. Many works reporting the conjugation of QDs with carbohydrates and lectins have been published, using different strategies and reagents. These bioconjugates enabled studies that are very sensitive and specific, with potential to detect and elucidate the glycode expressed in various normal or pathologic conditions. **GENERAL SIGNIFICANCE:** Produce a quick reference source over the main advances reached in the glyconanotechnology using QDs as fluorescent probes.

Dapkute, D., et al. (2017). "Skin-derived mesenchymal stem cells as quantum dot vehicles to tumors." *Int J Nanomedicine* **12**: 8129-8142.

**Purpose:** Cell-mediated delivery of nanoparticles is emerging as a new method of cancer diagnostics and treatment. Due to their inherent regenerative properties, adult mesenchymal stem cells (MSCs) are naturally attracted to wounds and sites of inflammation, as well as tumors. Such characteristics enable MSCs to be used in cellular hitchhiking of nanoparticles. In this study, MSCs extracted from the skin connective tissue were investigated as transporters of semiconductor nanocrystals quantum dots (QDs). **Materials and methods:** Cytotoxicity of carboxylated CdSe/ZnS QDs was assessed by lactate dehydrogenase

cell viability assay. Quantitative uptake of QDs was determined by flow cytometry; their intracellular localization was evaluated by confocal microscopy. In vitro tumor-tropic migration of skin-derived MSCs was verified by Transwell migration assay. For in vivo migration studies of QD-loaded MSCs, human breast tumor-bearing immunodeficient mice were used. **Results:** QDs were found to be nontoxic to MSCs in concentrations no more than 16 nM. The uptake studies showed a rapid QD endocytosis followed by saturating effects after 6 h of incubation and intracellular localization in the perinuclear region. In vitro migration of MSCs toward MDA-MB-231 breast cancer cells and their conditioned medium was up to nine times greater than the migration toward noncancerous breast epithelial cells MCF-10A. In vivo, systemically administered QD-labeled MSCs were mainly located in the tumor and metastatic tissues, evading most healthy organs with the exception being blood clearance organs (spleen, kidneys, liver). **Conclusion:** Skin-derived MSCs demonstrate applicability in cell-mediated delivery of nanoparticles. The findings presented in this study promise further development of a cell therapy and nanotechnology-based tool for early cancer diagnostics and therapy.

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.

Deglmann, C. J., et al. (2017). "Cadmium Telluride Quantum Dots as a Fluorescence Marker for Adipose Tissue Grafts." *Ann Plast Surg* **78**(2): 217-222.

Plastic and reconstructive surgeons increasingly apply adipose tissue grafting in a clinical setting, although the anticipation of graft survival is insecure. There are only few tools for tracking transplanted fat grafts in vivo. Murine adipose tissue clusters were incubated with negatively charged, mercaptopropionic acid-coated cadmium telluride quantum dots (QDs) emitting in the dark red or near infrared. The intracellular localization of QDs was studied by confocal laser scanning microscopy. As a result, the adipose tissue clusters showed a proportional increase in fluorescence with increasing concentrations (1, 10, 16, 30, 50 nM) of cadmium telluride QDs. Laser scanning microscopy demonstrated a membrane bound localization of QDs. Vacuoles and cell nuclei of adipocytes were spared by QDs. We conclude that QDs were for the first time proven intracellular in adult adipocytes and demonstrate a strong fluorescence signal. Therefore, they may play an essential role for in vivo tracking of fat grafts.

Deng, H., et al. (2017). "Quantum dots-labeled strip biosensor for rapid and sensitive detection of microRNA based on target-recycled nonenzymatic amplification strategy." *Biosens Bioelectron* **87**: 931-940.

MicroRNAs (miRNAs) have been proved to be potential biomarkers in early cancer diagnosis. It is of great significance for rapid and sensitive detection of miRNAs, particularly with point-of-care (POC) diagnosis. Herein, it is the first time to construct quantum dots (QDs)-labeled strip biosensor based on target-recycled nonenzymatic amplification strategy for miRNA detection. In the system, QDs were served as bright, photostable signal labels, which endow this biosensor with good detection efficiency. Moreover, a target-recycled amplification strategy relies on sequence-specific hairpins strand displacement process without the assistance of enzymes, was introduced to further improve the sensitivity. Meanwhile eliminating the requirement of environment-susceptible enzyme protein makes it easy to preserve and enhances the stability and reproducibility of this sensor. Benefiting from these outstanding characteristics, this platform exhibited a good detection sensitivity range from 2fmol to 200fmol with a limit of 200amol, using only 20μL of sample within 80min. The assay was also 10-fold more sensitive than that with a conventional colloidal gold-based test strip for miRNA detection. Additionally, the analysis of miRNA in various tumor cell extracts was in accordance with the performance of quantitative realtime polymerase chain reaction (qRT-PCR). Clinical tumor samples were also tested, and 16 of 20 samples gave out positive signals, which demonstrated the practical application capacity of the biosensor. Therefore, the proposed biosensor holds

great promise for potential POC applications and early cancer diagnosis.

Ding, D., et al. (2017). "MoO<sub>3-x</sub> 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, MoO<sub>3-x</sub> quantum dots (QDs). Due to their strong NIR harvesting ability, MoO<sub>3-x</sub> 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 MoO<sub>3-x</sub> QD mediated phototherapeutic group without obvious lesions to the major organs. In addition, the desired PT effect also makes MoO<sub>3-x</sub> 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 MoO<sub>3-x</sub> 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 characteristic fluorescence, respectively.

Duman, F. D., et al. (2017). "Folic acid-conjugated cationic Ag<sub>2</sub>S quantum dots for optical imaging and

selective doxorubicin delivery to HeLa cells." *Nanomedicine (Lond)* **12**(19): 2319-2333.

**AIM:** We aim to develop folic acid (FA)-conjugated cationic Ag<sub>2</sub>S near-infrared quantum dots (NIRQDs) for the delivery of doxorubicin (DOX) selectively to folate receptor (FR)-positive cancer cells to achieve enhanced drug efficacy and optical tracking in the NIR region. **MATERIALS & METHODS:** Cationic Ag<sub>2</sub>S NIRQDs were decorated with FA using a PEG bridge and loaded with DOX. In vitro studies were performed on FR-positive human cervical carcinoma cells and FR-negative A549 cells. **RESULTS:** Significantly higher uptake of DOX by human cervical carcinoma cells and a greater therapeutic effect along with a strong intracellular optical signal were obtained with DOX-loaded FA-conjugated Ag<sub>2</sub>S NIRQDs. **CONCLUSION:** These Ag<sub>2</sub>S NIRQDs are promising theranostic nanoparticles for receptor-mediated delivery of DOX with enhanced drug efficacy combined with optical imaging.

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.

Fakhri, A., et al. (2017). "Preparation and characterization of Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O 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 Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O 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 Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O QDs/Cellulose fibers nanocomposites indicate that the average diameter was 62.5nm. The Saturation magnetization (M<sub>s</sub>) indicates the Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O 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 Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O 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 Fe<sub>3</sub>O<sub>4</sub>-Ag<sub>2</sub>O quantum dots/cellulose fibers nanocomposites.

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.

Feng, H. and Z. Qian (2017). "Functional Carbon Quantum Dots: A Versatile Platform for Chemosensing and Biosensing." *Chem Rec*.

Carbon quantum dot has emerged as a new promising fluorescent nanomaterial due to its excellent optical properties, outstanding biocompatibility and accessible fabrication methods, and has shown huge application perspective in a variety of areas, especially in chemosensing and biosensing applications. In this personal account, we give a brief overview of carbon quantum dots from its origin and preparation methods, present some advance on fluorescence origin of carbon quantum dots, and focus on development of chemosensors and biosensors based on functional carbon quantum dots. Comprehensive advances on functional carbon quantum dots as a versatile platform for sensing from our group are included and summarized as well as some typical examples from the other groups. The biosensing applications of functional carbon quantum dots are highlighted from selective assays of enzyme activity to fluorescent identification of cancer cells and bacteria.

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 prognosis of human diseases or why function of single miRNA in cancer is rendered to oncomir or tumor 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, dyskeratosis 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 against cancer. It may also partly contribute to the elucidation of complex mechanisms and development of agents of anti-cancer.

Garcia-Cortes, M., et al. (2017). "Sensitive prostate specific antigen quantification using dihydrolipoic acid surface-functionalized phosphorescent quantum dots." *Anal Chim Acta* **987**: 118-126.

Herein, high-quality Mn-doped ZnS quantum dots (QDs) have been synthesized using a facile approach directly in aqueous media. The surface of the obtained QDs was further modified by cap-exchange of the native cysteine shell with dihydrolipoic acid (DHLA) ligands resulting in nanocrystals with high water-stability having an intense phosphorescent signal. Covalent bioconjugation of the DHLA-coated nanoparticles with an anti-IgG antibody was then carried out. Interestingly the QD immunoprobe (QD-labelled antibodies) maintained an intense phosphorescence emission, without any significant spectral-shift (as compared to the free QDs). Coupling of an asymmetric flow field flow fractionation technique to an elemental mass spectrometry detection enabled the accurate determination of the efficiency of the bioconjugation reaction. The obtained nanoparticle-antibody bioconjugate was then applied to develop a quantitative sandwich-type phosphorescent immunoassay for Prostate Specific Antigen (PSA), and a limit of detection (LOD) of 17 pg mL<sup>-1</sup> of PSA was achieved and allow to quantify such biomarker in samples within clinically relevant levels. Finally, the assay was validated for the quantification of PSA in the cellular media of prostate cancer cells. Obtained results proved the robustness of the proposed immunoassay based on long-lived phosphorescence measurements against eventual photoluminescent interferences significantly affecting the conventional short-lived fluorescence detection.

Ge, S., et al. (2017). "Ultrasensitive Photoelectrochemical Biosensing of Cell Surface N-Glycan Expression Based on the Enhancement of Nanogold-Assembled Mesoporous Silica Amplified by Graphene Quantum Dots and Hybridization Chain Reaction." *ACS Appl Mater Interfaces* **9**(8): 6670-6678.

An ultrasensitive photoelectrochemical (PEC) biosensor for N-glycan expression based on the enhancement of nanogold-assembled mesoporous silica nanoparticles (GMSNs) was fabricated, which also combined with multibranching hybridization chain reaction (mHCR) and graphene quantum dots (GQDs). In this work, the localized surface plasmon resonance, mHCR and GQDs-induced signal amplification strategies were integrated exquisitely and applied sufficiently. In the fabrication, after porous ZnO spheres immobilized on the Au nanorod-modified paper working electrode were sensitized by CdTe QDs, the GMSNs were assembled on the CdTe QDs. Then the photocurrent efficiency was improved by the sensitization of the CdTe QDs and the localized surface plasmon resonance of GMSNs. Successively, the products of mHCR with multiple biotins for multiple horseradish peroxidase binding and multiple branched arms for capturing the target cells were attached on the as-prepared electrode. The chemiluminescent (CL) emission with the aid of horseradish peroxidase served as an inner light source to excite photoactive materials for simplifying the instrument. Furthermore, the aptamer could capture the cancer cells by its highly efficient cell recognition ability, which avoided the conventional routing cell counting procedures. Meanwhile, the GQDs served as the signal amplification strategy, which was exerted in the process of N-glycan evaluation because the competitive absorption of exciting light and consumption of H<sub>2</sub>O<sub>2</sub> served as the electron donor of the PEC system and the oxidant of the luminol-based CL system. This judiciously engineered biosensor offered a promising platform for the exploration of N-glycan-based physiological processes.

Godina-Nava, J. J., et al. (2017). "Quantum mechanical model for the anticarcinogenic effect of extremely-low-frequency electromagnetic fields on early chemical hepatocarcinogenesis." *Phys Rev E* **95**(2-1): 022416.

Using the conventional Haberkorn approach, it is evaluated the recombination of the radical pair (RP) singlet spin state to study theoretically the cytoprotective effect of an extremely-low-frequency electromagnetic field (ELF-EMF) on early stages of hepatic cancer chemically induced in rats. The proposal is that ELF-EMF modulates the interconversion rate of singlet and triplet spin states of the RP populations modifying the products from the metabolization of carcinogens. Previously, we found that the daily treatment with ELF-EMF 120 Hz inhibited the number and area of preneoplastic lesions in chemical carcinogenesis. The singlet spin population is evaluated diagonalizing the spin density matrix through the Lanczos method in a radical pair mechanism (RPM). Using four values of the interchange energy, we have

studied the variations over the singlet population. The low magnetic field effect as a test of the influence over the enzymatic chemical reaction is evaluated calculating the quantum yield. Through a bootstrap technique the range is found for the singlet decay rate for the process. Applying the quantum measurements concept, we addressed the impact toward hepatic cells. The result contributes to improving our understanding of the chemical carcinogenesis process affected by charged particles that damage the DNA.

Goreham, R. V., et al. (2018). "Demonstration of the lack of cytotoxicity of unmodified and folic acid modified graphene oxide quantum dots, and their application to fluorescence lifetime imaging of HeCaT cells." *Mikrochim Acta* **185**(2): 128.

The authors describe the synthesis of water-soluble and fluorescent graphene oxide quantum dots via acid exfoliation of graphite nanoparticles. The resultant graphene oxide quantum dots (GoQDs) were then modified with folic acid. Folic acid receptors are overexpressed in cancer cells and hence can bind to functionalized graphene oxide quantum dots. On excitation at 305 nm, the GoQDs display green fluorescence with a peak wavelength at ~520 nm. The modified GoQDs are non-toxic to macrophage cells even after prolonged exposure and high concentrations. Fluorescence lifetime imaging and multiphoton microscopy was used (in combination) to image HeCaT cells exposed to GoQDs, resulting in a superior method for bioimaging. Graphical abstract Schematic representation of graphene oxide quantum dots, folic acid modified graphene oxide quantum dots (red), and the use of fluorescence lifetime to discriminate against green auto-fluorescence of HeCaT cells.

Grinyte, R., et al. (2016). "Microbead QD-ELISA: Microbead ELISA Using Biocatalytic Formation of Quantum Dots for Ultra High Sensitive Optical and Electrochemical Detection." *ACS Appl Mater Interfaces* **8**(43): 29252-29260.

Electrochemical detection strategies employing semiconductor quantum dots (QDs) open up new opportunities for highly sensitive detection of biological targets. We designed a new assay based on microbead linked enzymatic generation of CdS QDs (Microbead QD-ELISA) and employed it in optical and electrochemical affinity assays for the cancer biomarker superoxide dismutase 2 (SOD2). Biotinylated antibodies against SOD2 were immobilized on the surface of polyvinyl chloride microbeads bearing streptavidin. In order to prevent any non-specific adsorption the microbeads were further blocked with bovine serum albumin. The analyte, SOD2 was captured on microbeads and labeled with alkaline phosphatase-conjugated antibody linked

with mouse antibody against SOD2. Hydrolysis of para-nitrophenylphosphate by immobilized alkaline phosphatase triggered the rapid formation of phosphate-stabilized CdS QDs on the surface of microbeads. The resulting semiconductor nanoparticles were detected by fluorescence spectroscopy, microscopy, and square-wave voltammetry (SWV). The electrochemical assay based on the detection with square-wave voltammograms of Cd(2+) ions originating from immobilized CdS QDs showed linearity up to 45 ng mL(-1), and the limit of SOD2 detection equal to 0.44 ng mL(-1) (1.96 x 10(-11) M). This detection limit is lower by 2 orders of magnitude in comparison with that of other previously published assays for superoxide dismutase. The electrochemical assay was validated with HepG2 (Human hepatocellular carcinoma) cell lysate containing SOD2.

Gu, C. (2017). "Quantum dots-based fluorescence resonance energy transfer biosensor for monitoring cell apoptosis." *Luminescence* **32**(7): 1186-1191.

The development of advanced methods for accurately monitoring cell apoptosis has extensive significance in the diagnostic and pharmaceutical fields. In this study, we developed a rapid, sensitive and selective approach for the detection of cell apoptosis by combining the site-specific recognition and cleavage of the DEVD-peptide with quantum dots (QDs)-based fluorescence resonance energy transfer (FRET). Firstly, biotin-peptide was conjugated on the surface of AuNPs to form AuNPs-pep through the formation of an Au-S bond. Then, AuNPs-pep-QDs nanoprobe was obtained through the connection between AuNPs-pep and QDs. FRET is on and the fluorescence of QDs is quenched at this point. The evidence of UV-vis spectra, transmission electron microscopy (TEM), and Fourier transform infrared (FT-IR) spectroscopy revealed that the connection was successful. Upon the addition of apoptosis cell lysis solution, peptide was cleaved by caspase-3, and AuNPs was dissociated from the QDs. At this time, FRET is off, and thus the QDs fluorescence was recovered. The experimental conditions were optimized in terms of ratio of peptide to AuNPs, buffer solution, and the temperature of conjugation and enzyme reaction. The biosensor was successfully applied to distinguishing apoptosis cells and normal cells within 2 h. This study demonstrated that the biosensor could be utilized to evaluate anticancer drugs.

Gui, W., et al. (2017). "N-Doped graphene quantum dot@mesoporous silica nanoparticles modified with hyaluronic acid for fluorescent imaging of tumor cells and drug delivery." *Mikrochim Acta* **185**(1): 66.

The authors describe new bifunctional mesoporous silica nanoparticles (NPs) for specific

targeting of tumor cells and for intracellular delivery of the cancer drug doxorubicin (DOX). Mesoporous silica nanoparticles (MSNPs) were coated with blue fluorescent N-graphene quantum dots, loaded with the drug DOX, and finally coated with hyaluronic acid (HA). Cellular uptake of the NPs with an architecture of the type HA-DOX-GQD@MSNPs enabled imaging of human cervical carcinoma (HeLa) cells via fluorescence microscopy. The cytotoxicity of the nanoparticles on HeLa cells was also assessed. The results suggest that the NPs are higher cytotoxicity effect and exert in living cell imaging ability. Compared to the majority of other drug nanocarrier systems, the one described here enables simultaneous DOX release and fluorescent monitoring. Graphical abstract Schematic of the bifunctional mesoporous silica nanoparticles were obtained via the Stober method, along with the doxorubicin loaded and the hyaluronic acid capped. The sensor shows good specificity and significant cytotoxicity effect on Hela cells. (TEOS: tetraethyl orthosilicate; GQDs: graphene quantum dots; DOX: doxorubicin; HA: Hyaluronic acid).

Guo, J., et al. (2018). "Study of plasmonics in hybrids made from a quantum emitter and double metallic nanoshell dimer." *J Phys Condens Matter*.

We developed a theory for the fluorescence (FL) for quantum emitter and double metallic nanoshell dimer hybrids using the density matrix method. The dimer is made from two identical double metallic nanoshells, which are made of a dielectric core, a gold metallic shell and a dielectric spacer layer. The quantum emitters are deposited on the surface of the spacer layers of the dimers due to the electrostatic absorptions. We consider that dimer hybrids are surrounded by biological cells. This can be achieved by injecting them in human or animal cells. The surface plasmon polaritons are calculated for the dimer using Maxwell's equations in the static wave approximation. The calculated SPP energy agrees with experimental data of the dimer made from a silica core, a gold metallic nanoshell and a silica spacer layer. We have also obtained an analytical expression of the fluorescence using the density matrix method. We compare our theory with FL experimental data where the FL spectrum was measured by varying the thickness of the spacer layer from 9 nm to 40 nm. A good agreement between theory and experiment is found. We have showed that the enhancement of the fluorescence increases as the thickness of the spacer layer decreases. We have also found that the enhancement of the fluorescence increases as the distance between the double metallic nanoshells in the dimer decreases. These are interesting findings which are consistent with the experiments and can be used to

control the fluorescence enhancement in the fluorescence-based biomedical imaging and cancer treatment. These interesting findings may also be useful in the fabrication of nanosensors and nanoswitches for applications in medicine.

Guo, T., et al. (2018). "Black Phosphorus Quantum Dots with Renal Clearance Property for Efficient Photodynamic Therapy." *Small* **14**(4).

Black phosphorus (BP) nanomaterials have emerged as rapidly rising stars in the field of nanomedicine. In this work, BP quantum dots (BPQDs) are synthesized and their potential as photosensitizers is investigated for the first time. The BPQDs present good stability in physiological medium and no appreciable cytotoxicity. More importantly, the BPQDs can be rapidly eliminated from the body in their intact form via renal clearance due to their ultrasmall hydrodynamic diameter (5.4 nm). Both in vitro and in vivo studies indicate that the BPQDs have excellent photodynamic effect under light irradiation that can effectively generate reactive oxygen species to kill cancer cells. The BPQDs thus can serve as biocompatible and powerful photosensitizers for efficient photodynamic therapy.

Guo, W., et al. (2017). "Multifunctional Theranostic Agent of Cu<sub>2</sub>(OH)PO<sub>4</sub> 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 Cu<sub>2</sub>(OH)PO<sub>4</sub> quantum dots [denoted as Cu<sub>2</sub>(OH)PO<sub>4</sub>@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 Cu<sub>2</sub>(OH)PO<sub>4</sub>@PAA upon 1064-nm laser irradiation, with no detectable lesions in major organs during treatment. Meanwhile, Cu<sub>2</sub>(OH)PO<sub>4</sub>@PAA is also an exogenous contrast for photoacoustic tomography (PAT) imaging to depict



tumors under NIR irradiation. In brief, the Cu<sub>2</sub>(OH)PO<sub>4</sub>@PAA QDs prepared in this work are expected to serve as a multifunctional theranostic platform.

Hasanzadeh, M., et al. (2018). "Ultrasensitive electrochemical immunosensing of tumor suppressor protein p53 in unprocessed human plasma and cell lysates using a novel nanocomposite based on poly-cysteine/graphene quantum dots/gold nanoparticle." *Int J Biol Macromol* **107**(Pt A): 1348-1363.

An ultrasensitive electrochemical immunosensor for quantitation of tumor suppressor protein p53 based on ternary signal amplification strategy was fabricated. In this work, p53-antibody was immobilized onto a green and biocompatible nanocomposite containing poly l-cysteine (P-Cys) as conductive matrix and graphene quantum dots (GQDs)/gold nanoparticles (GNPs) as dual amplification elements. Therefore, a novel multilayer film based on P-Cys, GQDs, and GNPs was exploited to develop a highly sensitive immunosensor for detection of p53. Fully electrochemical methodology was used to prepare a new transducer on a gold surface which provided a high surface area to immobilize a high amount of the anti-p53. Under optimized condition the calibration curve for p53 concentration was linear up to 0.000197-0.016 pM (by SWV technique) and 0.195-50 pM (by DPV technique) with lower limit of quantification of 0.065 fM. Also, linear range and lower limit of quantification of p53 in unprocessed human plasma were 0.000592-1.296 pM and 0.065 fM, respectively. The method was applied to the assay of p53 in human plasma sample and normal and malignant cell line lysates such as normal cell Line from mouse C3H (L929), colon cancer cell-HCT, prostate cancer cell line PC-3, and human breast adenocarcinoma cell line-MCF7.

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 immunodevices? 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 immunoassay for ultrasensitive detection of breast cancer specific carbohydrate (CA-15-3) in unprocessed human plasma and MCF-7 breast cancer cell lysates using gold nanoparticle electrochemically assembled onto thiolated graphene quantum dots." *Int J Biol Macromol*.

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 nanoparticle (Au NPs) electrochemically assembled onto thiolated graphene quantum dots (CysA/GQDs) for the detection of CA 15-3 antibodies. The CysA/Au NPs/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 NPs' 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 NPs/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).

Hu, J., et al. (2017). "Single Quantum Dot-Based Nanosensor for Sensitive Detection of O-GlcNAc Transferase Activity." *Anal Chem* **89**(23): 12992-12999.

Protein glycosylation is a ubiquitous post-translational modification that plays crucial roles in modulating biological recognition events in development and physiology. Human O-GlcNAc transferase (OGT) is an intracellular enzyme responsible for O-linked N-acetylglucosamine (O-GlcNAc) glycosylation, and the deregulation of OGT

activity occurs in cancer, diabetes, and neurodegenerative disease. Here we develop a single quantum dot (QD)-based nanosensor for sensitive OGT assay. We design a Cy5/biotin-modified peptide with a serine hydroxyl group for sensing OGT and a protease site adjacent to the glycosylation site for proteinase cleavage, with a universal nonradioactive UDP-GlcNAc as the sugar donor and a Cy5/biotin-modified peptide as the substrate. In the presence of OGT, it catalyzes the glycosylation reaction to generate a glycosylated peptide that is a protease-protection peptide. The resultant glycosylated Cy5/biotin-modified peptides may assemble on the surface of the streptavidin-coated QD to obtain a QD-peptide-Cy5 nanostructure in which the fluorescence resonance energy transfer (FRET) from the QD to Cy5 can occur, leading to the emission of Cy5 which can be quantified by single-molecule detection. This method exhibits high sensitivity with a limit of detection of  $3.47 \times 10^{-13}$  M, and it is very simple and straightforward without the involvement of any enzyme purification, radioisotope-labeled sugar donors, specific antibodies, and the synthesis of fluorescent UDP-GlcNAc analogues. Moreover, this method can be used for enzyme kinetic analysis, quantitative detection of cellular OGT activity, and the screening of OGT inhibitors, holding great potential for further application in drug discovery and clinical diagnosis.

Hu, Z., et al. (2016). "Aqueous synthesized quantum dots interfere with the NF-kappaB pathway and confer anti-tumor, anti-viral and anti-inflammatory effects." *Biomaterials* **108**: 187-196.

The NF-kappaB pathway plays crucial roles in inflammatory responses and cell survival. Aberrant constitutive NF-kappaB activation is associated with various human diseases including cancer and inflammatory and auto-immune diseases. Consequently, it is highly desirable to develop new kinds of inhibitors, which are highly efficacious for blocking the NF-kappaB pathway. In this study, by using a typical kind of aqueous synthesized quantum dots (QDs), i.e., CdTe QDs, as a model, we for the first time demonstrated that the QDs could selectively affect the cellular nuclear factor-kappaB (NF-kappaB) signaling pathway, but do not affect the AKT or ERK pathways. Typically, the QDs efficiently inhibited the activation of IKKalpha and IKKbeta, resulting in the suppression of both the canonical and the non-canonical NF-kappaB signaling pathways. Inhibition of NF-kappaB by QDs downregulates anti-apoptotic genes and promotes apoptosis in cancer cells. The QDs induced NF-kappaB inhibition and cytotoxicity could be blocked by N-acetylcysteine due to the reduced cellular uptake of QDs. Importantly, inhibition of NF-kappaB by QDs displayed promising effects against the viral replication

and in vivo bacterial endotoxin-induced inflammatory responses. These data suggest the QDs as potent inhibitors of the NF-kappaB signaling pathway, both in vitro and in vivo. Our findings highlight the potential of using QDs in the development of anti-cancer, anti-viral, and anti-inflammatory approaches, and also facilitate better understanding of QDs-related cellular behavior under the molecular level.

Hua, X. W., et al. (2017). "Carbon quantum dots with intrinsic mitochondrial targeting ability for mitochondria-based theranostics." *Nanoscale* **9**(30): 10948-10960.

We prepare for the first time a novel type of fluorescent carbon quantum dot (or carbon dot, CD) with intrinsic mitochondrial targeting ability by a one-step hydrothermal treatment of chitosan, ethylenediamine and mercaptosuccinic acid. The as-prepared CDs can realize mitochondrial imaging and mitochondria-targeted photodynamic cancer therapy without further modifications of other mitochondriotropic ligands (such as triphenylphosphine, TPP). Currently, many commercial mitochondrial probes suffer from the lack of modifiable groups, poor photostability, short tracking time, high cost and/or complicated staining procedures, which severely limit their applications in live-cell mitochondrial imaging. Compared to commercial mitochondrial probes such as MitoTrackers, our CDs exhibit remarkable features including ultra-simple and cost-effective synthesis, excellent photostability, facile storage, easy surface modification, wash-free and long-term imaging capability and negligible cytotoxicity. Besides, since mitochondria are susceptible to the reactive oxygen species generated during chemo-, photo- or radiotherapy, mitochondria-targeted cancer therapy has attracted much attention due to its satisfying anticancer efficiency. To test if the CDs can be used for mitochondria-targeted drug delivery, they were conjugated with a photosensitizer rose bengal (RB) and the resultant CDs-RB nanomissiles achieved efficient cellular uptake and mitochondrial targeting/accumulation, realizing mitochondria-targeted photodynamic therapy. We believe that the CD-based nanotheranostics holds great promise in various biomedical applications.

Hua, X. W., et al. (2018). "Fluorescent Carbon Quantum Dots with Intrinsic Nucleolus-Targeting Capability for Nucleolus Imaging and Enhanced Cytosolic and Nuclear Drug Delivery." *ACS Appl Mater Interfaces* **10**(13): 10664-10677.

Nucleolus tracking and nucleus-targeted photodynamic therapy are attracting increasing attention due to the importance of nucleolus and the sensitivity of nucleus to various therapeutic stimuli.

Herein, a new class of multifunctional fluorescent carbon quantum dots (or carbon dots, CDs) synthesized via the one-pot hydrothermal reaction of m-phenylenediamine and l-cysteine was reported to effectively target nucleolus. The as-prepared CDs possess superior properties, such as low-cost and facile synthesis, good water dispersibility, various surface groups for further modifications, prominent photostability, excellent compatibility, and rapid/convenient/wash-free staining procedures. Besides, as compared with SYTO RNaselect (a commonly used commercial dye for nucleolus imaging) that can only image nucleolus in fixed cells, the CDs can realize high-quality nucleolus imaging in not only fixed cells but also living cells, allowing the real-time tracking of nucleolus-related biological behaviors. Furthermore, after conjugating with protoporphyrin IX (PpIX), a commonly used photosensitizer, the resultant CD-PpIX nanomissiles showed remarkably increased cellular uptake and nucleus-targeting properties and achieved greatly enhanced phototherapeutic efficiency because the nuclei show poor tolerance to reactive oxygen species produced during the photodynamic therapy. The *in vivo* experiments revealed that the negatively charged CD-PpIX nanomissiles could rapidly and specifically target a tumor site after intravenous injection and cause efficient tumor ablation with no toxic side effects after laser irradiation. It is believed that the present CD-based nanosystem will hold great potential in nucleolus imaging and nucleus-targeted drug delivery and cancer therapy.

Huang, N., et al. (2017). "Efficacy of NGR peptide-modified PEGylated quantum dots for crossing the blood-brain barrier and targeted fluorescence imaging of glioma and tumor vasculature." *Nanomedicine* **13**(1): 83-93.

Delivery of imaging agents to brain glioma is challenging because the blood-brain barrier (BBB) functions as a physiological checkpoint guarding the central nervous system from circulating large molecules. Moreover, the ability of existing probes to target glioma has been insufficient and needs to be improved. In present study, PEG-based long circulation, CdSe/ZnS quantum dots (QDs)-based nanoscale and fluorescence, asparagines-glycine-arginine peptides (NGR)-based specific CD13 recognition were integrated to design and synthesize a novel nanoprobe by conjugating biotinylated NGR peptides to avidin-PEG-coated QDs. Our data showed that the NGR-PEG-QDs were nanoscale with less than 100 nm and were stable in various pH (4.0~8.0). These nanomaterials with non-toxic concentrations could cross the BBB and target CD13-overexpressing glioma and tumor vasculature *in vitro* and *in vivo*, contributing to fluorescence imaging of this brain malignancy. These

achievements allowed groundbreaking technological advances in targeted fluorescence imaging for the diagnosis and surgical removal of glioma, facilitating potential transformation toward clinical nanomedicine.

Hwang, G., et al. (2017). "In situ imaging of quantum dot-AZD4547 conjugates for tracking the dynamic behavior of fibroblast growth factor receptor 3." *Int J Nanomedicine* **12**: 5345-5357.

Fibroblast growth factor receptors (FGFRs) play an important role in determining cell proliferation, differentiation, migration, and survival. Although a variety of small-molecule FGFR inhibitors have been developed for cancer therapeutics, the interaction between FGFRs and FGFR inhibitors has not been well characterized. The FGFR-inhibitor interaction can be characterized using a new imaging probe that has strong, stable signal properties for *in situ* cellular imaging of the interaction without quenching. We developed a kinase-inhibitor-modified quantum dot (QD) probe to investigate the interaction between FGFR and potential inhibitors. Especially, turbo-green fluorescent protein-FGFR3s were overexpressed in HeLa cells to investigate the colocalization of FGFR3 and AZD4547 using the QD-AZD4547 probe. The result indicates that this probe is useful for investigating the binding behaviors of FGFR3 with the FGFR inhibitor. Thus, this new inhibitor-modified QD probe is a promising tool for understanding the interaction between FGFR and inhibitors and for creating future high-content, cell-based drug screening strategies.

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. Faticah (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.

Jagminas, A., et al. (2017). "Methionine-mediated synthesis of magnetic nanoparticles and functionalization with gold quantum dots for theranostic applications." *Beilstein J Nanotechnol* **8**: 1734-1741.

Biocompatible superparamagnetic iron oxide nanoparticles (NPs) through smart chemical functionalization of their surface with fluorescent species, therapeutic proteins, antibiotics, and aptamers offer remarkable potential for diagnosis and therapy of

disease sites at their initial stage of growth. Such NPs can be obtained by the creation of proper linkers between magnetic NP and fluorescent or drug probes. One of these linkers is gold, because it is chemically stable, nontoxic and capable to link various biomolecules. In this study, we present a way for a simple and reliable decoration the surface of magnetic NPs with gold quantum dots (QDs) containing more than 13.5% of Au(+). Emphasis is put on the synthesis of magnetic NPs by co-precipitation using the amino acid methionine as NP growth-stabilizing agent capable to later reduce and attach gold species. The surface of these NPs can be further conjugated with targeting and chemotherapy agents, such as cancer stem cell-related antibodies and the anticancer drug doxorubicin, for early detection and improved treatment. In order to verify our findings, high-resolution transmission electron microscopy (HRTEM), atomic force microscopy (AFM), FTIR spectroscopy, inductively coupled plasma mass spectroscopy (ICP-MS), and X-ray photoelectron spectroscopy (XPS) of as-formed CoFe<sub>2</sub>O<sub>4</sub> NPs before and after decoration with gold QDs were applied.

Jarockyte, G., et al. (2018). "3D cellular spheroids as tools for understanding carboxylated quantum dot behavior in tumors." *Biochim Biophys Acta* **1862**(4): 914-923.

**BACKGROUND:** Monolayer cell cultures have been considered the most suitable technique for in vivo cellular experiments. However, a lot of cellular functions and responses that are present in natural tissues are lost in two-dimensional cell cultures. In this context, nanoparticle accumulation data presented in literature are often not accurate enough to predict behavior of nanoparticles in vivo. Cellular spheroids show a higher degree of morphological and functional similarity to the tissues. **METHODS:** Accumulation and distribution of carboxylated CdSe/ZnS quantum dots (QDs), chosen as model nanoparticles, was investigated in cellular spheroids composed of different phenotype mammalian cells. The findings were compared with the results obtained in in vivo experiments with human tumor xenografts in immunodeficient mice. The diffusive transport model was used for theoretical nanoparticles distribution estimation. **RESULTS:** QDs were accumulated only in cells, which were localized in the periphery of cellular spheroids. CdSe/ZnS QDs were shown to be stable and inert; they did not have any side-effects for cellular spheroids formation. Penetration of QDs in both cellular spheroids and in vivo tumor model was limited. The mathematical model confirmed the experimental results: nanoparticles penetrated only 25µm into cellular spheroids after 24h of incubation. **CONCLUSIONS:** Penetration of negatively charged

nanoparticles is limited not only in tumor tissue, but also in cellular spheroids. **GENERAL SIGNIFICANCE:** The results presented in this paper show the superior applicability of cellular spheroids to cell monolayers in the studies of the antitumor effect and penetration of nanomedicines.

Javanbakht, S. and H. Namazi (2018). "Doxorubicin loaded carboxymethyl cellulose/graphene quantum dot nanocomposite hydrogel films as a potential anticancer drug delivery system." *Mater Sci Eng C Mater Biol Appl* **87**: 50-59.

Creating anticancer properties in the hydrogel film could make it as a candidate for treating cancer tissues. In this work, a novel hydrogel nanocomposite films with anticancer properties were designed via incorporation of graphene quantum dot (GQD) as a nanoparticle into carboxymethyl cellulose (CMC) hydrogel and using doxorubicin (DOX) as drug model with broad-spectrum anticancer properties. Drug release studies carried out at two different pHs and the MTT assay was evaluated for DOX-loaded CMC/GQD nanocomposite hydrogel films against blood cancer cells (K562). The prepared nanocomposite hydrogel films were characterized using Fourier transform infrared (FT-IR), UV-Vis spectroscopy, scanning electron microscopy (SEM), permeability and mechanical properties. The prepared CMC/GQD nanocomposite hydrogel films showed an improvement in vitro swelling, degradation, water vapor permeability and pH-sensitive drug delivery properties along with not significant toxicity against blood cancer cells (K562). According to the obtained results, this nanocomposite hydrogel films can be proposed to use as an anticancer film and drug delivery system.

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.

Jha, S., et al. (2017). "Pharmaceutical potential of quantum dots." *Artif Cells Nanomed Biotechnol*: 1-9.

Quantum dots (QDs) or fluorescent nanocrystals are designed nanoparticles that are promising for several biological and bio-medical applications as well as drug delivery and simultaneous cellular imaging. QD's have exhibited promising potential primarily in receptor based targeting as a result of their distinctive physicochemical properties. Functionalized QDs (f-QDs) have been developed as effective, safe, nano-sized smart systems to deliver a wide range of bio-actives. Surface modified fluorescent carbon QDs with surface modification have attracted attention as targeting ligand to accomplish cellular targeting with enhanced specificity. Several surface engineered and conjugated fluorescent carbon QDs are presently being explored for the treatment of cancer and the outcome is eagerly awaited.

Johansson, M. P., et al. (2017). "New insight on the structural features of the cytotoxic auristatins MMAE and MMAF revealed by combined NMR spectroscopy and quantum chemical modelling." *Sci Rep* **7**(1): 15920.

Antibody-drug conjugates (ADCs) are emerging as a promising class of selective drug delivery systems in the battle against cancer and other diseases. The auristatins monomethyl auristatin E (MMAE) and monomethyl auristatin F (MMAF) appear as the cytotoxic drug in almost half of the state-of-the-art ADCs on the market or in late stage clinical trials. Here, we present the first complete NMR spectroscopic characterisation of these challenging molecules, and investigate their structural properties by a combined NMR and quantum chemical modelling approach. We find that in solution, half of the drug molecules are locked in an inactive conformation, severely decreasing their efficiency, and potentially increasing the risk of side-effects. Furthermore, we identify sites susceptible to future modification, in order to potentially improve the performance of these drugs.

Jose, A., et al. (2018). "Multifunctional fluorescent iron quantum clusters for non-invasive radiofrequency

ablation of 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  $\Delta T$  approximately 50 degrees C at concentrations as low as 165  $\mu\text{g}/\text{mL}$ . 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 up to 1000  $\mu\text{g}/\text{mL}$  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.

Khodadadei, F., et al. (2017). "Methotrexate-loaded nitrogen-doped graphene quantum dots nanocarriers as an efficient anticancer drug delivery system." *Mater Sci Eng C Mater Biol Appl* **79**: 280-285.

Graphene quantum dots (GQDs) are new efficient nanomaterials used in therapeutic applications. In this study, blue fluorescent nitrogen-doped GQDs (N-GQDs) were synthesized by a hydrothermal method via pyrolysis of citric acid as the carbon source and urea as the nitrogen source. The existence of doped nitrogen in GQDs was confirmed by FTIR characterization. Here, for the first time, the N-GQDs were loaded with the anticancer drug, methotrexate (MTX), to prepare MTX-(N-GQDs) as an efficient drug delivery system. The establishment of the strong pi-pi stacking interaction between MTX and N-GQDs was confirmed by FTIR and UV-vis spectroscopies indicating successful loading of MTX to N-GQDs. The in-vitro cytotoxicity of MTX-(N-GQDs) on human breast cancer cells investigated through MTT assay suggested that the drug-free N-GQDs nanocarriers are highly

biocompatible, whereas the MTX-loaded ones are more cytotoxic than the free MTX.

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 Au<sub>8</sub>, 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. 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.

Kimber, J. A. and S. G. Kazarian (2017). "Spectroscopic imaging of biomaterials and biological systems with FTIR microscopy or with quantum cascade lasers." *Anal Bioanal Chem* **409**(25): 5813-5820.

Spectroscopic imaging of biomaterials and biological systems has received increased interest within the last decade because of its potential to aid in the detection of disease using biomaterials/biopsy samples and to probe the states of live cells in a label-free manner. The factors behind this increased attention include the availability of improved infrared microscopes and systems that do not require the use of a synchrotron as a light source, as well as the decreasing costs of these systems. This article highlights the current technical challenges and future directions of mid-infrared spectroscopic imaging within this field. Specifically, these are improvements in spatial resolution and spectral quality through the use of novel added lenses and computational algorithms, as well as quantum cascade laser imaging systems, which offer advantages over traditional Fourier transform infrared systems with respect to the speed of acquisition and field of view. Overcoming these challenges will push forward spectroscopic imaging as a viable tool for disease diagnostics and medical research. Graphical abstract Absorbance images of a biopsy obtained using an FTIR imaging microscope with and without an added lens, and also using a QCL microscope with high-NA objective.

Kominkova, M., et al. (2017). "Comparative study on toxicity of extracellularly biosynthesized and laboratory synthesized CdTe quantum dots." *J Biotechnol* **241**: 193-200.

Nanobiosynthesis belongs to the most recent methods for synthesis of nanoparticles. This type of synthesis provides many advantages including the uniformity in particle shape and size. The biosynthesis has also a significant advantage regarding chemical properties of the obtained particles. In this study, we characterized the basic properties and composition of quantum dots (QDs), obtained by the extracellular biosynthesis by *Escherichia coli*. Furthermore, the toxicity of the biosynthesized QDs was compared to QDs prepared by microwave synthesis. The obtained results revealed the presence of cyan CdTe QDs after removal of substantial amounts of organic compounds, which stabilized the nanoparticle surface. QDs toxicity was evaluated using three cell lines Human Foreskin Fibroblast (HFF), Human Prostate Cancer cells (PC-3) and Breast Cancer cells (MCF-7) and the MTT assay. The test revealed differences in the toxicity between

variants of QDs, varying about 10% in the HFF and 30% in the MCF-7 cell lines. The toxicity of the biosynthesized QDs to the PC-3 cell lines was about 35% lower in comparison with the QDs prepared by microwave synthesis.

Labas, A., et al. (2017). "Combined Docking and Quantum Chemical Study on CYP-Mediated Metabolism of Estrogens in Man." *Chem Res Toxicol* **30**(2): 583-594.

Long-term exposure to estrogens seriously increases the incidence of various diseases including breast cancer. Experimental studies indicate that cytochrome P450 (CYP) enzymes catalyze the bioactivation of estrogens to catechols, which can exert their harmful effects via various routes. It has been shown that the 4-hydroxylation pathway of estrogens is the most malign, while 2-hydroxylation is considered a benign pathway. It is also known experimentally that with increasing unsaturation of ring B of estrogens the prevalence of the 4-hydroxylation pathway significantly increases. In this study, we used a combination of structural analysis, docking, and quantum chemical calculations at the B3LYP/6-311+G\* level to investigate the factors that influence the regioselectivity of estrogen metabolism in man. We studied the structure of human estrogen metabolizing enzymes (CYP1A1, CYP1A2, CYP1B1, and CYP3A4) in complex with estrone using docking and investigated the susceptibility of estrone, equilin, and equilenin (which only differ in the unsaturation of ring B) to undergo 2- and 4-hydroxylation using several models of CYP enzymes (Compound I, methoxy, and phenoxy radical). We found that even the simplest models could account for the experimental difference between the 2- and 4- hydroxylation pathways and thus might be used for fast screening purposes. We also show that reactivity indices, specifically in this case the radical and nucleophilic condensed Fukui functions, also correctly predict the likeliness of estrogen derivatives to undergo 2- or 4-hydroxylation.

Lai, P. Y., et al. (2017). "Aqueous synthesis of Ag and Mn co-doped In<sub>2</sub>S<sub>3</sub>/ZnS quantum dots with tunable emission for dual-modal targeted imaging." *Acta Biomater* **50**: 522-533.

Here, we present the microwave-assisted synthesis of In<sub>2</sub>S<sub>3</sub>/ZnS core/shell quantum dots (QDs) co-doped with Ag(+) and Mn(2+) (referred to as AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS). Ag(+) altered the optical properties of the host QDs, whereas the spin magnetic moment (S=5/2) of Mn(2+) efficiently induced the longitudinal relaxation of water protons. To the best of our knowledge, this is the first report of the aqueous synthesis of color-tunable AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS core/shell QDs with magnetic properties. The synthetic procedure

is rapid, facile, reproducible, and scalable. The obtained QDs offered a satisfactory quantum yield (45%), high longitudinal relaxivity ( $6.84s(-1)mM(-1)$ ), and robust photostability. In addition, they exhibited excellent stability over a wide pH range (5-12) and high ionic strength (0.15-2.0M NaCl). As seen by confocal microscopy and magnetic resonance imaging, AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS conjugated to hyaluronic acid (referred to as AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS@HA) efficiently and specifically targeted cluster determinant 44, a receptor overexpressed on cancer cells. Moreover, AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS@HA showed negligible cytotoxicity in vitro and in vivo, rendering it a promising diagnostic probe for dual-modal imaging in clinical applications.

**STATEMENT OF SIGNIFICANCE:** In this manuscript, we reported a facile and rapid method to prepare In<sub>2</sub>S<sub>3</sub>/ZnS core/shell quantum dots (QDs) co-doped with Ag(+) and Mn(2+) (referred to as AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS). Ag(+) dopants were used to alter the optical properties of the In<sub>2</sub>S<sub>3</sub> host, whereas Mn(2+) co-dopants with their unpaired electrons provided paramagnetic properties. The emission wavelength of the core/shell QDs could be tuned from 550 to 743nm with a maximum PL quantum yield of 45%. The resulting core/shell QDs also maintained a stable emission in aqueous solution at broad ranges of pH (5-12) and ionic strength (0.15-2.0M NaCl), as well as a high photostability under continuous irradiation. In vivo cytotoxicity experiments showed that up to 500µg/mL AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS@HA did not cause obvious toxicity to zebrafish embryos. In vitro targeted cell luminescence and magnetic resonance imaging showed that AgMn:In<sub>2</sub>S<sub>3</sub>/ZnS conjugated to hyaluronic acid was selectively and efficiently internalized in CD44-expressing tumor cells, confirming that the resultant QDs could function as dual-modal imaging probes for accurate diagnosis.

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.

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.

The 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 SOCl<sub>2</sub> 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 carcinoembryonic 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, 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. (2017). "Recent Advance in the Cancer Bioimaging with Graphene Quantum Dots." Curr Med Chem.

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, M. M., et al. (2017). "Effects of arginine-glycine-aspartic acid peptide-conjugated quantum dots-induced photodynamic therapy on pancreatic carcinoma in vivo." Int J Nanomedicine **12**: 2769-2779.

Quantum dots (QDs) conjugated with integrin antagonist arginine-glycine-aspartic acid (RGD) peptides (QDs-RGD) are novel nanomaterials with a unique optical property: a high molar extinction coefficient. Previously, we have shown that QDs-RGD demonstrate a photodynamic therapy (PDT) effect as new photosensitizers for the pancreatic cancer cell line SW1990 in vitro. Here, we investigate the application of QDs-RGD in mice bearing pancreatic tumors using PDT. To ensure that more photosensitizers accumulated in tumors, QDs-RGD were injected intratumorally. After selection of an adequate dosage for injection from analyses of biodistribution images captured by an IVIS system, PDT was initiated. Three groups were created according to different PDT

procedures. In group 1, mice were injected with QDs-RGD intratumorally, and an optical fiber connected to a laser light was inserted directly into the tumor. Irradiation was sustained for 20 min with a laser light (630 nm) at 100 mW/cm<sup>2</sup>. In group 2, the laser optical fiber was placed around, and not inserted into, tumors. In group 3, PDT was conducted as in group 1 but without injection of QDs-RGD. After 28 days of observation, tumors on the back of mice in group 1 grew slowly ( $V/V_0 = 3.24 \pm 0.70$ ) compared with the control groups, whose tumors grew quickly, and the mean  $V/V_0$  reached  $6.08 \pm 0.50$  (group 2) and  $7.25 \pm 0.82$  (group 3). Histology of tumor tissues showed more necrotic tissues, more inflammatory cells, and less vascular tissue in the PDT group than those in the control groups. These results suggest that QDs-RGD-mediated PDT, with illumination using an optical fiber inserted directly into the tumor, can inhibit the growth of SW1990 tumors with high efficiency in nude mice.

Li, S., et al. (2017). "Exceptionally High Payload of the IR780 Iodide on Folic Acid-Functionalized Graphene Quantum Dots for Targeted Photothermal Therapy." ACS Appl Mater Interfaces **9**(27): 22332-22341.

The IR780 iodide (IR780) is recognized as an effective theranostic agent for simultaneous near-infrared fluorescence imaging and photothermal therapy (PTT). However, the rigid chloro-cyclohexenyl ring makes IR780 insoluble in almost all pharmaceutically acceptable solvents, which inevitably limits its clinical application. We report folic acid (FA)-functionalized graphene quantum dots (GQDs-FA) containing a large and intact sp<sup>2</sup> domain with carboxyl groups around the edge. Such GQDs-FA possess exceptionally high loading capacity for IR780 via strong pi-pi stacking interactions, and the water solubility of IR780 is improved by over 2400-fold after loading onto GQDs-FA (IR780/GQDs-FA). IR780/GQDs-FA with an improved photostability, an enhanced tumor-targeting ability, and a high photothermal conversion efficiency of 87.9% were capable of producing sufficient hyperthermia to effectively kill cancer cells and completely eradicate tumors upon 808 nm laser irradiation. The present IR780/GQDs-FA may open up great opportunities for the effective PTT to treat cancer.

Li, W. Q., et al. (2018). "Mitochondria-based aircraft carrier enhances in vivo imaging of carbon quantum dots and delivery of anticancer drug." Nanoscale **10**(8): 3744-3752.

The application of engineered bacteria-based drug delivery vehicles to treat cancer has been practiced for more than a century. Mitochondria, evolutionarily originated from bacteria, are ubiquitous, semi-autonomous cellular organelles. In this study, we

present the first exploration of using mitochondria as a delivery system of carbon quantum dots (CQDs) for in vivo imaging and administration of the anticancer drug doxorubicin (DOX). The results show that mitochondria as carriers are compatible with CQD loading and preserve the optical properties of CQDs. Moreover, the mitochondria delivery system can improve the CQD bio-distribution in organs and prolong the retention time of CQDs after intravenous injection. Furthermore, mitochondria loaded with doxorubicin hydrochloride (Mito-DOX) show an enhanced therapeutic effect compared to free DOX. The mitochondria-based "aircraft" system may be a promising novel therapeutic platform with high potential for biological imaging and drug delivery to fight cancer and other diseases.

Li, X., et al. (2017). "Simultaneous detection of MCF-7 and HepG2 cells in blood by ICP-MS with gold nanoparticles and quantum dots as elemental tags." *Biosens Bioelectron* **90**: 343-348.

In this work, we demonstrate a novel method based on inductively coupled plasma mass spectrometry (ICP-MS) detection with gold nanoparticles (Au NPs) and quantum dots (QDs) labeling for the simultaneous counting of two circulating tumor cell lines (MCF-7 and HepG2 cells) in human blood. MCF-7 and HepG2 cells were captured by magnetic beads coupled with anti-EpCAM and then specifically labeled by CdSe QDs-anti-ASGPR and Au NPs-anti-MUC1, respectively, which were used as signal probes for ICP-MS measurement. Under the optimal experimental conditions, the limits of detection of 50 MCF-7, 89 HepG2 cells and the linear ranges of 200-40000 MCF-7, 300-30000 HepG2 cells were obtained, and the relative standard deviations for seven replicate detections of 800 MCF-7 and HepG2 cells were 4.6% and 5.7%, respectively. This method has the advantages of high sensitivity, low sample consumption, wide linear range and can be extended to the simultaneous detection of multiple CTC lines in human peripheral blood.

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, 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.

Lin, G., et al. (2017). "Quantum Dots-siRNA Nanoplexes for Gene Silencing in Central Nervous System Tumor Cells." *Front Pharmacol* **8**: 182.

RNA interfering (RNAi) using short interfering RNA (siRNA) is becoming a promising approach for cancer gene therapy. However, owing to the lack of safe and efficient carriers, the application of RNAi for clinical use is still very limited. In this study, we have developed cadmium sulphoselenide/Zinc sulfide quantum dots (CdSSe/ZnS QDs)-based nanocarriers for in vitro gene delivery. These CdSSe/ZnS QDs are functionalized with polyethyleneimine (PEI) to form stable nanoplex (QD-PEI) and subsequently they are used for siRNA loading which specially targets human telomerase reverse transcriptase (TERT). High gene transfection efficiency

(>80%) was achieved on two glioblastoma cell lines, U87 and U251. The gene expression level (49.99 +/- 10.23% for U87, 43.28 +/- 9.66% for U251) and protein expression level (51.58 +/- 7.88% for U87, 50.69 +/- 7.59% for U251) of TERT is observed to decrease substantially after transfecting the tumor cells for 48 h. More importantly, the silencing of TERT gene expression significantly suppressed the proliferation of glioblastoma cells. No obvious cytotoxicity from these QD-PEI nanoplexes were observed over at 10 times of the transfected doses. Based on these results, we envision that QDs engineered here can be used as a safe and efficient gene nanocarrier for siRNA delivery and a promising tool for future cancer gene therapy applications.

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, M. X., et al. (2017). "One-Pot Aqueous Synthesis of Near-Infrared Quantum Dots for Bioimaging and Photodynamic Therapy of Gliomas." *Acta Neurochir Suppl* **124**: 303-308.

**BACKGROUND:** As the early detection and total destruction of gliomas are essential for longer survival, we attempted to synthesize a quantum dot (QD) that is capable of recognizing glioma cells for imaging and photodynamic therapy. **METHODS:** Using a one-pot aqueous approach, near infrared-emitting CdTe was produced. After detection of its physicochemical characteristics, it was conjugated with RGD. The emission images were observed with confocal microscopy. To test its toxicity, CdTe-RGD at

various concentrations was separately added to a human glioma cell line (U251) and a mouse embryo fibroblast cell line (3T3) (control) for incubation in dark conditions. To test its photodynamic effect, the U251 and 3T3 cells were then irradiated for 5-60 min, using a 632.8-nm laser. **RESULTS:** This QD (Phi = 3.75 nm, photoluminescence (PL) peak wavelength = 700 nm, photoluminescence quantum yield (PLQY) = 20 %), was a spherical crystal with excellent monodispersity. Under a confocal microscope, U251 cells were visualized, but not the 3T3 cells. In dark conditions, the survival rates of both U251 and 3T3 cells were above 85 %. After laser irradiation, the survival rate of U251 cells decreased to 37 +/- 1.6 % as the irradiation time and the CdTe-RGD concentration were increased. **CONCLUSIONS:** With good physicochemical characteristics and low toxicity, this QD-RGD has broad prospects for use in the biomedical imaging and photodynamic therapy of gliomas.

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, W., et al. (2018). "Confined Synthesis of Carbon Nitride in a Layered Host Matrix with Unprecedented Solid-State Quantum Yield and Stability." *Adv Mater* **30**(2).

Fluorescent carbon nanomaterials have drawn tremendous attention for their intriguing optical performances, but their employment in solid-state luminescent devices is rather limited as a result of aggregation-induced photoluminescence quenching. Herein, ultrathin carbon nitride (CN) is synthesized within the 2D confined region of layered double hydroxide (LDH) via triggering the interlayer condensation reaction of citric acid and urea. The resulting CN/LDH phosphor emits strong cyan light under UV-light irradiation with an absolute solid-state quantum yield (SSQY) of 95.9 +/- 2.2%, which is, to the best of our knowledge, the highest value of carbon-based fluorescent materials ever reported. Furthermore, it exhibits a strong luminescence stability toward temperature, environmental pH, and photocorrosion. Both experimental studies and theoretical calculations reveal that the host-guest interactions between the rigid LDH matrix and interlayer carbon nitride give the predominant contribution to the unprecedented SSQY and stability. In addition, prospective applications of the CN/LDH material are demonstrated in both white light-emitting diodes and upconversion fluorescence imaging of cancer cells.

Liu, X., et al. (2017). "In vivo cation exchange in quantum dots for tumor-specific imaging." *Nat Commun* **8**(1): 343.

In vivo tumor imaging with nanoprobe suffers from poor tumor specificity. Here, we introduce a nanosystem, which allows selective background quenching to gain exceptionally tumor-specific signals. The system uses near-infrared quantum dots and a membrane-impermeable etchant, which serves as a cation donor. The etchant rapidly quenches the quantum dots through cation exchange (ionic etching), and facilitates renal clearance of metal ions released from the quantum dots. The quantum dots are intravenously delivered into orthotopic breast and pancreas tumors in mice by using the tumor-penetrating iRGD peptide. Subsequent etching quenches excess quantum dots, leaving a highly tumor-specific signal provided by the intact quantum dots remaining in the extravascular tumor cells and fibroblasts. No toxicity is noted. The system also facilitates the detection of peritoneal tumors with high specificity upon intraperitoneal tumor targeting and selective etching of excess untargeted quantum dots. In vivo cation exchange may be a promising strategy to enhance specificity of tumor imaging. The imaging of tumors in vivo using nanoprobe has been challenging due to the lack of sufficient tumor specificity. Here, the authors develop a tumor-specific quantum dot system that permits in vivo cation exchange to achieve selective background quenching and high tumor-specific imaging.

Liu, X., et al. (2017). "Core-shell structured polypyrrole/mesoporous SiO<sub>2</sub> nanocomposite capped with graphene quantum dots as gatekeeper for irradiation-controlled release of methotrexate." *Mater Sci Eng C Mater Biol Appl* **81**: 206-212.

A core-shell structured nanocomposite of polypyrrole/mesoporous SiO<sub>2</sub> (PPy/mSiO<sub>2</sub>) is rationally designed as the nanocarrier for methotrexate (MTX), a chemotherapeutic drug for cancer treatment. Graphene quantum dots (GQDs) are introduced to the outer surface of PPy/mSiO<sub>2</sub>, and it functions as a gatekeeper for the loaded MTX through the formation of H-bonds with the functionalized mSiO<sub>2</sub>. In the proposed nanocarrier for MTX, the mesopores in mSiO<sub>2</sub> are beneficial for the accommodation of MTX, resulting in enhanced encapsulation capacity of the nanocarrier; on the other hand, PPy can effectively convert the near-infrared (NIR) light to heat. Under the irradiation of NIR light, the H-bonds between GQDs and mSiO<sub>2</sub> are broken due to the gradually increased temperature, and therefore the GQDs cap is removed and consequently the encapsulated MTX is released from the nanocarrier. In this study, NIR irradiation-controlled drug delivery is achieved successfully owing to the synergistic effects of PPy, mSiO<sub>2</sub> and GQDs, which opens a new window for the construction of smart drug delivery systems.

Liu, Y., et al. (2017). "Construction of EGFR peptide gefitinib/quantum dots long circulating polymeric liposomes for treatment and detection of nasopharyngeal carcinoma." *Biochem Biophys Res Commun* **490**(2): 141-146.

Gefitinib/Quantum dots (QDs) loaded peptide long circulating liposomes (G/QDs-P-LCPL) were successfully prepared for treatment and detection by fluorescence labeling for nasopharyngeal carcinoma. Gefitinib was found to have marked inhibition which is dose- and time-dependent. Hoechst 33258 fluorescence staining and wound-healing assay indicated that as G/QDs-P-LCPL concentration increased, HONE1 staining cells decreased, while the amount of nucleus pyknosis and karyorrhexis grew. Fluorescence tracing result shows that the drug mainly distributed through tumors. G-P-LCPL target the HONE1 cells and significantly increase the drug uptake efficiency so as to improve the cells inhibit rate compared with the non-targeting group. The EGFR peptide LCPL are potentially useful for drug and fluorescence labeled delivery applications.

Lu, X., et al. (2018). "Glucose functionalized carbon quantum dot containing organic radical for optical/MR dual-modality bioimaging." *Mater Sci Eng C Mater Biol Appl* **82**: 190-196.

The organic paramagnetic compounds nitroxides have great potential as magnetic resonance imaging (MRI) contrast agents. Herein, we report the synthesis and characterization of glucose modified carbon quantum dot containing 2,2,6,6-tetramethylpiperidinoxy (TEMPO) for targeted bimodal MR/optical imaging of tumor cells. CQD-TEMPO-Glu shows the greatest potentials for bioimaging applications in view of low cytotoxicity, good biocompatibility, green fluorescence emission and high T1 relaxivities. The in vitro MR and optical imaging results confirm enhanced cellular internalization of CQD-TEMPO-Glu in cancer cells through GLUT mediated endocytosis. These results confirm that CQD-TEMPO-Glu is expected to be widely exploited as dual-modal contrast for cancer imaging.

Luo, C., et al. (2017). "Graphene Quantum Dots Downregulate Multiple Multidrug-Resistant Genes via Interacting with Their C-Rich Promoters." *Adv Healthc Mater* **6**(21).

Multidrug resistance (MDR) is the major factor in the failure of many forms of chemotherapy, mostly due to the increased efflux of anticancer drugs that mediated by ATP-binding cassette (ABC) transporters. Therefore, inhibiting ABC transporters is one of effective methods of overcoming MDR. However, high enrichment of ABC transporters in cells and their broad substrate spectra made to circumvent MDR are almost insurmountable by a single specific ABC transporter inhibitor. Here, this study demonstrates that graphene quantum dots (GQDs) could downregulate the expressions of P-glycoprotein, multidrug resistance protein MRP1, and breast cancer resistance protein genes via interacting with C-rich regions of their promoters. This is the first example that a single reagent could suppress multiple MDR genes, suggesting that it will be possible to target multiple ABC transporters simultaneously with a single reagent. The inhibitory ability of the GQDs to these drug-resistant genes is validated further by reversing the doxorubicin resistance of MCF-7/ADR cells. Notably, GQDs have superb chemical and physical properties, unique structure, low toxicity, and high biocompatibility; hence, their capability of inhibiting multiple drug-resistant genes holds great potential in cancer therapy.

Ma, B., et al. (2017). "Prolonged fluorescence lifetime of carbon quantum dots by combining with hydroxyapatite nanorods for bio-applications." *Nanoscale* **9**(6): 2162-2171.

Carbon quantum dots (CQDs) are a new type of fluorescent nanoparticle for cell imaging and tracking. However, they would easily diffuse and quench, followed by the loss of their fluorescence

ability. By connecting their functional groups with other nanoparticles, the CQDs will be protected from destruction and exhibit long-time fluorescence. Here, carbon quantum dot-hydroxyapatite (CQD-HAp) hybrid nanorods were prepared by the self-assembly of CQDs on the surface of HAp nanorods through a facile one-pot process. The morphology and size of the CQD-HAp hybrid nanorods can be well controlled by using oleic acid, which meanwhile is the source of CQDs. The hydrophilic CQD-HAp hybrid nanorods have prolonged fluorescence life due to the connection between CQDs and HAp nanorods, and exhibit a higher fluorescence quantum yield than pure CQDs. In addition, when hybrid nanorods load doxorubicin (Dox) to form Dox-CQD-HAp hybrid nanorods, they can more efficiently kill human cervical cancer (HeLa) cells, rather than human prostatic cancer (PC-3) cells. Long time fluorescence for cell imaging and high efficiency in killing cancer cells as a drug-delivery medium make CQD-HAp hybrid nanorods have great potential applications in the bio-field.

Madhankumar, A. B., et al. (2017). "Interleukin-13 conjugated quantum dots for identification of glioma initiating cells and their extracellular vesicles." *Acta Biomater* **58**: 205-213.

Cadmium selenide (CdSe) based quantum dots modified with polyethylene glycol and chemically linked to interleukin-13 (IL13) were prepared with the aim of identifying the high affinity receptor (IL13Ralpha2) which is expressed in glioma stem cells and exosomes secreted by these cancer stem cells. IL13 conjugated quantum dots (IL13QD) were thoroughly characterized for their physicochemical properties including particle size and surface morphology. Furthermore, the specific binding of the IL13QD to glioma cells and to glioma stem cells (GSC) was verified using a competitive binding study. The exosomes were isolated from the GSC conditioned medium and the expression of IL13Ralpha2 in the GSC and exosomes was verified. The binding property of IL13QD to the tumor associated exosomes was initially confirmed by transmission electron microscopy. The force of attraction between the quantum dots and U251 glioma cells and the exosomes was investigated by atomic force microscopy, which indicated a higher force of binding interaction between the IL13QD and IL13Ralpha2 expressing glioma cells and exosomes secreted by glioma stem cells. Flow cytometry of the IL13QD and exosomes from the culture media and cerebrospinal fluid (CSF) of patients with glioma tumors indicated a distinctly populated complex pattern different from that of non-targeted quantum dots and bovine serum albumin (BSA) conjugated quantum dots confirming specific binding potential of the IL13QD to the tumor associated exosomes. The results of this

study demonstrate that IL13QD can serve as an ex vivo marker for glioma stem cells and exosomes that can inform diagnosis and prognosis of patients harboring malignant disease. **STATEMENT OF SIGNIFICANCE:** Functionalized quantum dots are flexible semiconductor nanomaterials which have an immense application in biomedical research. In particular, when they are functionalized with biomolecules like proteins or antibodies, they have the specialized ability to detect the expression of receptors and antigens in cells and tissues. In this study we designed a cytokine (interleukin-13) functionalized quantum dot to detect a cancer associated receptor expressed in cancer stem cells and the extracellular vesicles (exosomes) secreted by the cancer cells themselves. The binding pattern of these cytokine modified quantum dots to the cancer stem cells and exosomes alters the physical properties of the complex in the fixed and suspended form. This altered binding pattern can be monitored by a variety of techniques, including transmission electron microscopy, atomic force microscopy and flow cytometry, and subsequent characterization of this quantum dot binding profile provides useful data that can be utilized as a fingerprint to detect cancer disease progression. This type of functionalized quantum dot fingerprint is especially useful for invasive cancers including brain and other metastatic cancers and may allow for earlier detection of disease progression or recurrence, thus saving the lives of patients suffering from this devastating disease.

Maity, A. R. and D. Stepensky (2017). "Nuclear and perinuclear targeting efficiency of quantum dots depends on density of peptidic targeting residues on their surface." *J Control Release* **257**: 32-39.

Targeted delivery to the cell nucleus can enhance the efficiency of drugs with nuclear site of action (some anti-cancer agents, DNA drugs, etc.), and can reduce their toxicity. Such targeting can be attained using nano-drug delivery systems (nano-DDSs) decorated with nuclear targeting sequences (such as nuclear localization sequence peptides, NLS). Several types of nano-DDSs decorated with NLS peptides were designed, but their investigation usually did not include quantitative analysis of the decoration efficiency and its correlation with the nano-DDSs intracellular localization. Thus, the major mechanisms and limiting factors of the nano-DDSs nuclear targeting are largely unknown yet. In this study, we report quantitative data for specific nano-formulation (CdSe-ZnS quantum dots) that include the efficiencies of its decoration with NLS residues and of its nuclear and perinuclear targeting, and demonstrate correlation between these parameters. For instance, QDs decorated with 83, 246, and 265 NLS peptides accumulated efficiently in the nucleus of HeLa cells or its vicinity (an average of 30.4%, 43.3%,

and 49.0% of the intracellular QDs, respectively). On the other hand, QDs decorated with 63, 231, and 308 scrambled peptides accumulated in the nucleus of HeLa cells or its vicinity to a much lower extent (an average of 17.3%, 21.1%, and 25.5% of the intracellular QDs, respectively). Thus, results of our study provide important insights into the structure-activity correlations (i.e., the relationships between the formulation properties and the intracellular fate of nano-DDSs) of nuclear-targeted drug delivery. We plan to apply the research tools that were developed in the course of this and our previous studies to investigate the nuclear and perinuclear targeting activities of different NLS sequences, and to investigate the effects of nano-DDSs size, charge, shape, decoration efficiency with nuclear targeting sequences, and other structural factors on nuclear and perinuclear targeting efficiency.

Manshian, B. B., et al. (2017). "Personalized medicine and follow-up of therapeutic delivery through exploitation of quantum dot toxicity." *Biomaterials* **127**: 1-12.

Tumor therapy using nanoparticles (NPs) is mainly aimed at using the NPs as carriers for therapeutic drugs or as mediators for external stimuli to generate heat. Recent studies have shown that the toxicity of NPs can also be specifically exploited to kill cancer cells. In the present work, we employ core-only CdTe quantum dots and study their cytotoxicity using a validated high-content screening approach. The data revealed a clear correlation between toxicity and quantum dot degradation, which could be monitored through loss of fluorescence intensity. Based on the in vitro data obtained, the in vivo dose was calculated relative to the estimated number of tumor cells based on luminescence measurements. The obtained results show a clear increase in reproducibility of the therapeutic effect compared to normal conditions, where a set dose of quantum dots was administered regardless of the tumor size. The therapeutic delivery could also be monitored in vivo, where the loss of fluorescence intensity correlated with the anticancer efficacy. The present work highlights the benefits of noninvasive imaging to monitor therapeutic delivery and to optimize treatment via personalized medicine.

Mansur, A. A., 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 (CMC) 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 ( $2r=4-5\text{nm}$ ) and hydrodynamic diameters ( $<15\text{nm}$ ) 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 nanoplateforms for cancer cell bioimaging and diagnosis purposes.

Mansur, A. A., et al. (2016). "Surface biofunctionalized CdS and ZnS quantum dot nanoconjugates for nanomedicine and oncology: to be or not to be nanotoxic?" *Int J Nanomedicine* **11**: 4669-4690.

Herein, for the first time, we demonstrated that novel biofunctionalized semiconductor nanomaterials made of Cd-containing fluorescent quantum dot nanoconjugates with the surface capped by an aminopolysaccharide are not biologically safe for clinical applications. Conversely, the ZnS-based nanoconjugates proved to be noncytotoxic, considering all the parameters investigated. The results of in vitro cytotoxicity were remarkably dependent on the chemical composition of quantum dot (CdS or ZnS), the nature of the cell (human cancerous and embryonic types), and the concentration and time period of exposure to these nanomaterials, caused by the effects of Cd(2+) on the complex nanotoxicity pathways involved in cellular uptake. Unexpectedly, no decisive evidence of nanotoxicity of CdS and ZnS conjugates was observed in vivo using intravenous injections in BALB/c mice for 30 days, with minor localized fluorescence detected in liver tissue specimens. Therefore, these results proved that CdS nanoconjugates could pose an excessive threat for clinical applications due to unpredicted and uncorrelated in vitro and in vivo responses caused by highly toxic cadmium ions at biointerfaces. On the contrary, ZnS nanoconjugates proved that the "safe by design" concept used in this research (ie, biocompatible core-shell nanostructures) could benefit a plethora of applications in nanomedicine and oncology.

Mansur, A. A. P., et al. (2017). "One-Pot Aqueous Synthesis of Fluorescent Ag-In-Zn-S Quantum

Dot/Polymer Bioconjugates for Multiplex Optical Bioimaging of Glioblastoma Cells." *Contrast Media Mol Imaging* **2017**: 3896107.

Cancer research has experienced astonishing advances recently, but cancer remains a major threat worldwide. Glioblastoma (GBM) is the most malignant brain tumor, where the early diagnosis is vital for longer survival. Thus, this study reports the synthesis of novel water-dispersible ternary AgInS<sub>2</sub> (AIS) and quaternary AgInS<sub>2</sub>-ZnS (ZAIS) fluorescent quantum dots using carboxymethylcellulose (CMC) as ligand for multiplexed bioimaging of malignant glioma cells (U-87 MG). Firstly, AgInS<sub>2</sub> core was prepared using a one-pot aqueous synthesis stabilized by CMC at room temperature and physiological pH. Then, an outer layer of ZnS was grown and thermally annealed to improve their optical properties and split the emission range, leading to core-shell alloyed nanostructures. Their physicochemical and optical properties were characterized, demonstrating that luminescent monodispersed AIS and ZAIS QDs were produced with average sizes of 2.2 nm and 4.3 nm, respectively. Moreover, the results evidenced that they were cytocompatible using in vitro cell viability assays towards human embryonic kidney cell line (HEK 293T) and U-87 MG cells. These AIS and ZAIS successfully behaved as fluorescent nanoprobe (red and green, resp.) allowing multiplexed bioimaging and biolabeling of contained glioma cells using confocal microscopy.

Mareeswari, P., et al. (2016). "Rhizopus stolonifer mediated biosynthesis of biocompatible cadmium chalcogenide quantum dots." *Enzyme Microb Technol* **95**: 225-229.

We report an efficient method to biosynthesize biocompatible cadmium telluride and cadmium sulphide quantum dots from the fungus *Rhizopus stolonifer*. The suspension of the quantum dots exhibited purple and greenish-blue luminescence respectively upon UV light illumination. Photoluminescence spectroscopy, X-ray diffraction, and transmission electron microscopy confirms the formation of the quantum dots. From the photoluminescence spectrum the emission maxima is found to be 424 and 476nm respectively. The X-ray diffraction of the quantum dots matches with results reported in literature. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay for cell viability evaluation carried out on 3-days transfer, inoculum  $3 \times 10^5$  cells, embryonic fibroblast cells lines shows that more than 80% of the cells are viable even after 48h, indicating the biocompatible nature of the quantum dots. A good contrast in imaging has been obtained upon incorporating the quantum dots in

human breast adenocarcinoma Michigan Cancer Foundation-7 cell lines.

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

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.

Mendieta-Moreno, J. I., et al. (2016). "Quantum Mechanics/Molecular Mechanics Free Energy Maps and Nonadiabatic Simulations for a Photochemical Reaction in DNA: Cyclobutane Thymine Dimer." *J Phys Chem Lett* **7**(21): 4391-4397.

The absorption of ultraviolet radiation by DNA may result in harmful genetic lesions that affect DNA replication and transcription, ultimately causing mutations, cancer, and/or cell death. We analyze the most abundant photochemical reaction in DNA, the cyclobutane thymine dimer, using hybrid quantum mechanics/molecular mechanics (QM/MM) techniques and QM/MM nonadiabatic molecular dynamics. We find that, due to its double helix structure, DNA presents a free energy barrier between nonreactive and reactive conformations leading to the photolesion. Moreover, our nonadiabatic simulations show that most of the photoexcited reactive conformations return to standard B-DNA conformations after an ultrafast nonradiative decay to the ground state. This work highlights the importance of dynamical effects (free

energy, excited-state dynamics) for the study of photochemical reactions in biological systems.

Misra, R., et al. (2017). "Backbone Engineered gamma-Peptide Amphitropic Gels for Immobilization of Semiconductor Quantum Dots and 2D Cell Culture." *Langmuir* **33**(31): 7762-7768.

We are reporting a spontaneous supramolecular assembly of backbone engineered gamma-peptide scaffold and its utility in the immobilization of semiconductor quantum dots and in cell culture. The stimulating feature of this gamma-peptide scaffold is that it efficiently gels both aqueous phosphate buffers and aromatic organic solvents. A comparative and systematic investigation reveals that the greater spontaneous self-aggregation property of gamma-peptide over the alpha- and beta-peptide analogues is mainly due to the backbone flexibility, increased hydrophobicity, and pi-pi stacking of gamma-phenylalanine residues. The hydrogels and organogels obtained from the gamma-peptide scaffold have been characterized through field emission scanning electron microscopy (FE-SEM), transmission electron microscopy (TEM), FT-IR, circular dichroism (CD), wide-angle X-ray diffraction, and rheometric study. Additionally, the peptide hydrogel has displayed a stimuli-responsive and thixotropic signature, which leads to the injectable hydrogels. 2D cell culture studies using normal and cancer cell lines reveal the biocompatibility of gamma-peptide hydrogels. Further, the immobilization of semiconductor core-shell quantum dots in the transparent gamma-peptide organogels showed ordered arrangement of quantum dots along the peptide fibrillar network with retaining photophysical property. Overall, gamma-peptide scaffolds may serve as potential templates for the design of new functional biomaterials.

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.

Monton, H., et al. (2017). "Rapid on-chip apoptosis assay on human carcinoma cells based on annexin-V/quantum dot probes." *Biosens Bioelectron* **94**: 408-414.

Despite all the efforts made over years to study the cancer expression and the metastasis event, there is not a clear understanding of its origins and effective treatment. Therefore, more specialized and rapid techniques are required for studying cell behaviour under different drug-based treatments. Here we present a quantum dot signalling-based cell assay carried out in a segmental microfluidic device that allows studying the effect of anti-cancer drugs in cultured cell lines by monitoring phosphatidylserine translocation that occurs in early apoptosis. The developed platform combines the automatic generation of a drug gradient concentration, allowing exposure of cancer cells to different doses, and the immunolabeling of the apoptotic cells using quantum dot reporters. Thereby a complete cell-based assay for efficient drug screening is performed showing a clear correlation between drug dose and amount of cells undergoing apoptosis.

Moulick, A., et al. (2017). "Using CdTe/ZnSe core/shell quantum dots to detect DNA and damage to DNA." *Int J Nanomedicine* **12**: 1277-1291.

CdTe/ZnSe core/shell quantum dot (QD), one of the strongest and most highly luminescent nanoparticles, was directly synthesized in an aqueous medium to study its individual interactions with important nucleobases (adenine, guanine, cytosine, and thymine) in detail. The results obtained from the optical analyses indicated that the interactions of the QDs with different nucleobases were different, which

reflected in different fluorescent emission maxima and intensities. The difference in the interaction was found due to the different chemical behavior and different sizes of the formed nanoconjugates. An electrochemical study also confirmed that the purines and pyrimidines show different interactions with the core/shell QDs. Based on these phenomena, a novel QD-based method is developed to detect the presence of the DNA, damage to DNA, and mutation. The QDs were successfully applied very easily to detect any change in the sequence (mutation) of DNA. The QDs also showed their ability to detect DNAs directly from the extracts of human cancer (PC3) and normal (PNT1A) cells (detection limit of 500 pM of DNA), which indicates the possibilities to use this easy assay technique to confirm the presence of living organisms in extreme environments.

Mu, X., et al. (2017). "Black Phosphorus Quantum Dot Induced Oxidative Stress and Toxicity in Living Cells and Mice." *ACS Appl Mater Interfaces* **9**(24): 20399-20409.

Black phosphorus (BP), as an emerging successor to layered two-dimensional materials, has attracted extensive interest in cancer therapy. Toxicological studies on BP are of great importance for potential biomedical applications, yet not systemically explored. Herein, toxicity and oxidative stress of BP quantum dots (BPQDs) at cellular, tissue, and whole-body levels are evaluated by performing the systemic in vivo and in vitro experiments. In vitro investigations show that BPQDs at high concentration (200  $\mu\text{g}/\text{mL}$ ) exhibit significant apoptotic effects on HeLa cells. In vivo investigations indicate that oxidative stress, including lipid peroxidation, reduction of catalase activity, DNA breaks, and bone marrow nucleated cells (BMNC) damage, can be induced by BPQDs transiently but recovered gradually to healthy levels. No apparent pathological damages are observed in all organs, especially in the spleen and kidneys, during the 30-day period. This work clearly shows that BPQDs can cause acute toxicities by oxidative stress responses, but the inflammatory reactions can be recovered gradually with time for up to 30 days. Thus, BPQDs do not give rise to long-term appreciable toxicological responses.

Muroski, M. E., et al. (2017). "Fatty Acid Uptake in T Cell Subsets Using a Quantum Dot Fatty Acid Conjugate." *Sci Rep* **7**(1): 5790.

Fatty acid (FA) metabolism directly influences the functional capabilities of T cells in tumor microenvironments. Thus, developing tools to interrogate FA-uptake by T cell subsets is important for understanding tumor immunosuppression. Herein, we have generated a novel FA-Qdot 605 dye conjugate

with superior sensitivity and flexibility to any of the previously commercially available alternatives. For the first time, we demonstrate that this nanoparticle can be used as a specific measure of fatty acid uptake by T cells both in-vitro and in-vivo. Flow cytometric analysis shows that both the location and activation status of T cells determines their FA uptake. Additionally, CD4+ Foxp3+ regulatory T cells (Tregs) uptake FA at a higher rate than effector T cell subsets, supporting the role of FA metabolism for Treg function. Furthermore, we are able to simultaneously detect glucose and fatty acid uptake directly within the tumor microenvironment. Cumulatively, our results suggest that this novel fluorescent probe is a powerful tool to understand FA utilization within the tumor, thereby providing an unprecedented opportunity to study T cell FA metabolism in-vivo.

Na, W., et al. (2016). "Highly sensitive detection of acid phosphatase by using a graphene quantum dots-based forster resonance energy transfer." *Talanta* **161**: 469-475.

A novel and effective fluorescence strategy was developed for sensitive and selective detection of acid phosphatase (ACP). A forster resonance energy transfer (FRET) biosensor was established by attaching Nile Red (NR) to graphene quantum dots (GQDs) via lecithin/beta-Cyclodextrin (lecithin/beta-CD) complex as the linker. The introduction of lecithin/beta-CD would bring GQDs-NR pair close enough through both electrostatic interaction and hydrophobic interaction, thereby making the FRET occur and thus resulting in the fluorescence quenching of GQDs (donor) and meanwhile the fluorescence enhancement of NR (acceptor). The presence of ACP in the sensing system would catalyze the hydrolysis of lecithin into two parts, resulting in the GQDs-NR pair separation. Meanwhile, considerable fluorescence recovery of GQDs and decreasing of NR was observed due to the inhibition of FRET progress. In this method, the limit of detection (LOD) is 28 microU/mL(-1) which was considerably low for ACP detection. Using the GQDs-based fluorescence biosensor, we successfully performed in vitro imaging of human prostate cancer cells.

Naderi, S., et al. (2018). "Cadmium telluride quantum dots induce apoptosis in human breast cancer cell lines." *Toxicol Ind Health*: 748233718763517.

**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.

Namdari, P., et al. (2017). "Synthesis, properties and biomedical applications of carbon-based quantum dots: An updated review." *Biomed Pharmacother* **87**: 209-222.

Carbon-based quantum dots (CQDs) are a newly developed class of carbon nano-materials that have attracted much interest and attention as promising competitors to already available semiconductor quantum dots owing to their un-comparable and unique

properties. In addition, controllability of QDs unique physiochemical properties is as a result of their surface passivation and functionalization. This is an update article (between 2013 and 2016) on the recent progress, characteristics and synthesis methods of QDs and different advantages in varieties of applications.

Narayanan, S., et al. (2017). "Phytaspase-loaded, Mn-doped ZnS quantum dots when embedded into chitosan nanoparticles leads to improved chemotherapy of HeLa cells using in cisplatin." *Biotechnol Lett* **39**(10): 1591-1598.

**OBJECTIVES:** To investigate the potential of recombinant phytaspase loaded manganese (Mn) doped zinc sulphide (ZnS) quantum dots embedded chitosan nanoparticles for augmenting cisplatin induced chemotherapy of HeLa cells. **RESULTS:** The recombinant phytaspase was cloned into bacterial expression vector PGEX-4T-2. The expressed and purified recombinant plant phytaspase protein from *Escherichia coli* BL21 was immobilized onto the cationic nanocomposite. Confocal microscopy elucidated the delivery of these luminescent nanocomposites inside cervical cancer HeLa cells. A 50% reduction in the viability of HeLa cells was achieved only in the case of phytaspase-nanocomposites-cisplatin combination at a dose of phytaspase (42 nM), nanocomposites (56.3 µg/ml) and cisplatin (0.44 µg/ml). **CONCLUSION:** Luminescent cationic nanocomposites were developed for intracellular delivery of recombinant phytaspase, which due to its caspase-like activity assisted in substantiating the chemotherapeutic activity of apoptosis inducing drug-cisplatin.

Nie, G., et al. (2018). "A graphene quantum dots based electrochemiluminescence immunosensor for carcinoembryonic antigen detection using poly(5-formylindole)/reduced graphene oxide nanocomposite." *Biosens Bioelectron* **101**: 123-128.

A novel electrochemiluminescence (ECL) immunosensor for ultrasensitive detection of carcinoembryonic antigen (CEA) was developed using signal amplification strategy based on poly(5-formylindole)/reduced graphene oxide nanocomposite (P5FIn/erGO) and Au nanoparticle (AuNP) decorated graphene quantum dots (GQDs) (GQDs@AuNP). As an effective matrix for immobilization of primary antibody (Ab1), P5FIn/erGO nanocomposite facilitated the ion transport during the redox reactions and provided larger surface areas for the immobilization of Ab1. GQDs@AuNP was used as labels to conjugate with secondary antibody (Ab2), which improved electron transfer capability with stable ECL intensity. The multiple amplification of P5FIn/erGO and GQDs@AuNP made the ECL immunosensor have a

broad linear range from 0.1pgmL(-1) to 10ngmL(-1) and a low detection limit with 3.78fgmL(-1). In addition, this ECL immunosensor performed with admirable stability and good selectivity and reproducibility as well. When this immunosensor was used for the analysis of CEA in human serum, good recoveries were obtained. Thus, there will be a promising future in the early diagnosis of cancer to detect CEA.

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.

Oksuzoglu, E., et al. (2017). "Antitumor activities on HL-60 human leukemia cell line, molecular docking, and quantum-chemical calculations of some sulfonamide-benzoxazoles." *Artif Cells Nanomed Biotechnol* **45**(7): 1388-1396.

We previously synthesized some novel benzoxazole derivatives-containing sulfonamide. In this study, the compounds were investigated for their antitumor activities against the HL-60 human leukemia cells, using the MTT assay. Moreover, quantum chemical calculations using the DFT methods were applied for understanding the difference in antitumor activity. Additionally, molecular docking into active

site of the DNA Topo II enzyme was performed on 3QX3. PDB file in order to find out possible mechanism of antitumor effect. According to all obtained results showed that compounds 1b, 1c, and 1d could be potential drug candidates as new antitumor agents, and are promising for cancer therapy.

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 $\pm$ 1.61nm, 0.17 $\pm$ 0.04 and -0.22 $\pm$ -0.03mV, respectively. The particles were spheroid-like in shape with relatively smooth surface. A higher EE (80.70 $\pm$ 2.11%) and DL (4.68 $\pm$ 0.04%) were recorded. The coloaded NLC exhibited a biphasic pattern of drug release. IC50 value was found to be 1.05 $\pm$ 0.58 $\mu$ M. 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.

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 extravascular 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.

Parani, S., et al. (2018). "Gelatin stabilization of quantum dots for improved stability and biocompatibility." *Int J Biol Macromol* **107**(Pt A): 635-641.

We herein report an aqueous synthesis of gelatin stabilized CdTe/CdS/ZnS (CSSG) core/double shell quantum dots (QDs) with improved biocompatibility. The as-synthesized QDs were characterized by ultraviolet-visible (UV-vis) and photoluminescence (PL) spectroscopic techniques, x-ray diffraction technique (XRD), x-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM). The CSSG QDs revealed high photoluminescence quantum yield (PLQY) with excellent stability over a period of one year and retained 90% of its initial PLQY without any aggregation or precipitation under ambient condition. The cell viability study conducted on HeLa, cervical cancer cell lines indicated that the gelatin stabilization effectively decreased the QDs cytotoxicity by about 50%. The CSSG QDs were conjugated with transferrin (Tf) for the efficient delivery to the cancer cells followed by fluorescence imaging. The results showed that the CSSG QDs illuminates the entire cell which renders the QDs as cell labeling markers. The gelatin stabilized core/double shell QDs are potential candidates for long time fluorescent bio-imaging.

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.

Pati, M. L., et al. (2018). "Quantum Dot Based Luminescent Nanoprobes for Sigma-2 Receptor Imaging." *Mol Pharm* **15**(2): 458-471.

The increasing importance of sigma-2 receptor as target for the diagnosis and therapy of tumors paves the way for the development of innovative optically traceable fluorescent probes as tumor cell contrast and therapeutic agents. Here, a novel hybrid organic-inorganic nanostructure is developed by combining the superior fluorescent properties of inorganic quantum dots (QDs), coated with a hydrophilic silica shell (QD@SiO<sub>2</sub> NPs), the versatility of the silica shell, and the high selectivity for sigma-2 receptor of the two synthetic ligands, namely, the 6-[(6-aminohexyl)oxy]-2-(3-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)propyl)-3,4-dihydroisoquinolin-1(2H)-one (MLP66) and 6-[1-[3-(4-cyclohexylpiperazin-1-yl)propyl]-1,2,3,4-tetrahydronaphthalen-5-yloxy] hexylamine (TA6). The proposed nanostructures represent a challenging alternative to all previously studied organic small fluorescent molecules, based on the same sigma-2 receptor affinity moieties. Flow cytometry and confocal fluorescence microscopy experiments, respectively, on fixed and living cancerous MCF7 cells, which overexpress the sigma-2 receptor, prove the ability of functionalized (QD@SiO<sub>2</sub>-TA6 and QD@SiO<sub>2</sub>-MLP66) NPs to be internalized and demonstrate their affinity to the sigma-2 receptor, ultimately validating the targeting properties conveyed to the NPs by sigma-2 ligand conjugation. The presented QD-based nanoprobes possess a great potential as in vitro selective sigma-2 receptor imaging agent and, consequently, could provide a significant impact to future theranostic applications.

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.

Peynshaert, K., et al. (2017). "Coating of Quantum Dots strongly defines their effect on lysosomal health and autophagy." *Acta Biomater* **48**: 195-205.

In the last decade the interest in autophagy got an incredible boost and the phenomenon quickly turned into an extensive research field. Interestingly, dysfunction of this cytoplasmic clearance system has been proposed to lie at the root of multiple diseases including cancer. We therefore consider it crucial from a toxicological point of view to investigate if nanomaterials that are developed for biomedical applications interfere with this cellular process. Here, we study the highly promising 'gradient alloyed' Quantum Dots (QDs) that differ from conventional ones by their gradient core composition which allows for better fluorescent properties. We carefully examined the toxicity of two identical gradient alloyed QDs, differing only in their surface coatings, namely 3-mercaptopropionic (MPA) acid and polyethylene glycol (PEG). Next to more conventional toxicological endpoints like cytotoxicity and oxidative stress, we examined the influence of these QDs on the autophagy pathway. Our study shows that the cellular effects induced by QDs on HeLa cells were strongly dictated by the surface coat of the otherwise identical particles. MPA-coated QDs proved to be highly biocompatible as a result of lysosomal activation and ROS reduction, two cellular responses that help the cell to cope with nanomaterial-induced stress. In contrast, PEGylated QDs were significantly more toxic due to increased ROS production and lysosomal impairment. This impairment next results in autophagy dysfunction which likely adds to their toxic effects. Taken together, our study shows that coating QDs with MPA is a better strategy than PEGylation for long term cell tracking with minimal cytotoxicity. **STATEMENT OF SIGNIFICANCE:** Gradient alloyed Quantum Dots (GA-QDs) are highly promising nanomaterials for biomedical imaging seeing they exhibit supremely fluorescent properties over conventional QDs. The translation of these novel QDs to the clinic requires a detailed toxicological examination, though the data on this is very limited. We therefore applied a systematic approach to examine the toxicity of GA-QDs coated with two commonly applied surface ligands, this while focusing on the autophagy pathway. The impact of QDs on this pathway is of importance since it has been connected with various diseases, including cancer. Our data accentuates that the coating defines the impact on autophagy and therefore the toxicity induced by QDs on cells: while MPA coated QDs were highly biocompatible, PEGylated QDs were toxic.

Pillai, S. S., et al. (2017). "Forster Resonance Energy Transfer Mediated Photoluminescence Quenching in Stoichiometrically Assembled CdSe/ZnS Quantum Dot-Peptide Labeled Black Hole Quencher Conjugates for Matrix Metalloproteinase-2 Sensing." *Anal Sci* **33**(2): 137-142.

The steady state and time-resolved photoluminescence quenching of streptavidin modified CdSe/ZnS quantum dots (QDs) instigated by biotin-peptide-BHQ-1 (biotin-pep-BHQ-1) molecule was investigated. Here, we have achieved an efficient photoluminescence (PL) quenching of QDs with the conjugation of dark quencher (black hole quencher-BHQ) molecules intermediated with the GPLGVRGK peptide. The luminescence of streptavidin-QDs585 was decreased upon titration with a nano molar concentration of the biotin-GPLGVRGK-BHQ-1 molecule. It has been suggested that the decrease of QDs PL occurred through a Forster resonance energy transfer (FRET) mechanism from the analysis of steady state photoluminescence intensity measurements as well as time resolved lifetime measurements of streptavidin-QDs and QDs-(pep-BHQ-1)<sub>n</sub> conjugates. The sequence of intermediate peptide GPLG downward arrowVRGK can act as a target material for matrix metalloproteinases-2 (MMP-2) produced by cancer cells at its Gly and Val region, shown by the down-headed arrow. Interestingly, here the reported self-assembled QDs-(pep-BHQ-1)<sub>n</sub> conjugates could detect the presence MMP-2 at a detection limit of 1 ng/mL with a clear luminescence recovery.

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<sup>-1</sup>, 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.

Pohanka, M. (2017). "Quantum Dots in the Therapy: Current Trends and Perspectives." *Mini Rev Med Chem* **17**(8): 650-656.

**BACKGROUND:** Quantum dots are an emerging nanomaterial with broad use in technical disciplines; however, their application in the field of biomedicine becomes also relevant and significant possibilities have appeared since the discovery in 1980s. **OBJECTIVE:** The current review is focused on the therapeutic applications of quantum dots which become an emerging use of the particles. They are introduced as potent carriers of drugs and as a material well suited for the diagnosis of disparate pathologies like visualization of cancer cells or pathogenic microorganisms. **CONCLUSION:** Quantum dots toxicity and modifications for the toxicity reduction are discussed here as well. Survey of actual papers and patents in the field of quantum dots use in the biomedicine is provided.

Qiu, Y., et al. (2017). "Novel Single-Cell Analysis Platform Based on a Solid-State Zinc-Coordinated 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-coordinated 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.

Radhika, R., et al. (2017). "Role of 6-Mercaptopurine in the potential therapeutic targets DNA base pairs and G-quadruplex DNA: insights from quantum chemical and molecular dynamics simulations." *J Biomol Struct Dyn*: 1-33.

The theoretical studies on DNA with the anticancer drug 6-Mercaptopurine (6-MP) are investigated using theoretical methods to shed light on drug designing. Among the DNA base pairs considered, 6-MP is stacked with GC with the highest interaction energy of -46.19 kcal/mol. Structural parameters revealed that structure of the DNA base pairs is deviated from the planarity of the equilibrium position due to the formation of hydrogen bonds and stacking interactions with 6-MP. These deviations are verified through the systematic comparison between X-H bond contraction and elongation and the associated blue shift and red shift values by both NBO analysis and vibrational analysis. Bent's rule is verified for the C-H bond contraction in the 6-MP interacted base pairs. The AIM results disclose that the higher values of electron density ( $\rho$ ) and Laplacian of electron density ( $\nabla^2\rho$ ) indicate the increased overlap between the orbitals that represent the strong interaction and positive values of the total electron density show the closed-shell interaction. The relative sensitivity of the chemical shift values for the DNA base pairs with 6-MP is investigated to confirm the hydrogen bond strength. Molecular dynamics simulation studies of G-quadruplex DNA d(TGGGGT)<sub>4</sub> with 6-MP revealed that the incorporation of 6-MP appears to cause local distortions and destabilize the G-quadruplex DNA.

Ramos-Gomes, F., et al. (2018). "Single- and two-photon imaging of human micrometastases and disseminated tumour cells with conjugates of nanobodies and quantum dots." *Sci Rep* **8**(1): 4595.

Early detection of malignant tumours and, especially, micrometastases and disseminated tumour cells is still a challenge. In order to implement highly sensitive diagnostic tools we demonstrate the use of nanoprobe engineered from nanobodies (single-domain antibodies, sdAbs) and fluorescent quantum dots (QDs) for single- and two-photon detection and imaging of human micrometastases and disseminated tumour cells in ex vivo biological samples of breast

and pancreatic metastatic tumour mouse models expressing human epidermal growth factor receptor 2 (HER2) or carcinoembryonic antigen (CEA). By staining thin (5-10 microm) paraffin and thick (50 microm) agarose tissue sections, we detected HER2- and CEA-positive human tumour cells infiltrating the surrounding tissues or metastasizing to different organs, including the brain, testis, lung, liver, and lymph nodes. Compared to conventional fluorescently labelled antibodies the sdAb-HER2-QD and sdAb-CEA-QD nanoprobe are superior in detecting micrometastases in tissue sections by lower photobleaching and higher brightness of fluorescence signals ensuring much better discrimination of positive signals versus background. Very high two-photon absorption cross-sections of QDs and small size of the nanoprobe ensure efficient imaging of thick tissue sections unattainable with conventional fluorescent probes. The nanobody-QD probes will help to improve early cancer diagnosis and prognosis of progression by assessing metastasis.

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.

Rodzic, L., et al. (2017). "Novel fluorescent CdTe quantum dot-thymine conjugate-synthesis, properties

and possible application." *Nanotechnology* **28**(4): 045701.

Novel, highly fluorescent cadmium telluride quantum dots conjugated with thymine and stabilized with thioglycolic acid were obtained and characterized. Successful formation of the conjugate was confirmed by elemental analysis, and UV-vis, fluorescence and Fourier transform infrared spectroscopies. Crystal structure and composition of the conjugates were characterized with x-ray diffraction and x-ray photoelectron spectroscopy. The size of the conjugates was 4-6 nm as demonstrated using atomic force microscopy and high resolution transmission electron microscopy imaging. The plasmon resonance fluorescence band at 540 nm on excitation at 351 nm was observed for these nanoparticles. The intensity of this band increased with the increase in the amount of conjugated thymine with no shift in its position. Based on the fluorescence measurements it was found that the CdTe-thymine conjugate interacted efficiently and selectively not only with adenine, a nucleobase complementary to thymine, but also with adenine-containing modified nucleosides, i.e., 5'-deoxy-5'-(methylthio)adenosine and 2'-O-methyladenosine, the urinary tumor markers which allow monitoring of the disease progression. To the best of our knowledge, as yet, there have been no studies presented in literature on that type of the interaction with CdTe-thymine conjugates. Therefore, the system presented can be considered as a working component of a selective adenine/adenosine biosensor with potential application in cancer diagnosis.

Sang, F., et al. (2018). "Quantum dots for a high-throughput Pfu polymerase based multi-round polymerase chain reaction (PCR)." *Analyst* **143**(5): 1259-1267.

Multi-round PCR is an important technique for obtaining enough target DNA from rare DNA resources, and is commonly used in many fields including forensic science, ancient DNA analysis and cancer research. However, multi-round PCR is often aborted, largely due to the accumulation of non-specific amplification during repeated amplifications. Here, we developed a Pfu polymerase based multi-round PCR technique assisted by quantum dots (QDs). Different PCR assays, DNA polymerases (Pfu and Taq), DNA sizes and GC amounts were compared in this study. In the presence of QDs, PCR specificity could be retained even in the ninth-round amplification. Moreover, the longer and more complex the targets were, the earlier the abortion happened in multi-round PCR. However, no obvious enhancement of specificity was found in multi-round PCR using Taq DNA polymerase. Significantly, the fidelity of Pfu polymerase based multi-round PCR was not sacrificed



in the presence of QDs. Besides, pre-incubation at 50 degrees C for an hour had no impact on multi-round PCR performance, which further authenticated the hot start effect of QDs modulated in multi-round PCR. The findings of this study demonstrated that a cost-effective and promising multi-round PCR technique for large-scale and high-throughput sample analysis could be established with high specificity, sensibility and accuracy.

Sansalone, L., et al. (2016). "Semiconductor Quantum Dots with Photoresponsive Ligands." Top Curr Chem (Cham) **374**(5): 73.

Photochromic or photocaged ligands can be anchored to the outer shell of semiconductor quantum dots in order to control the photophysical properties of these inorganic nanocrystals with optical stimulations. One of the two interconvertible states of the photoresponsive ligands can be designed to accept either an electron or energy from the excited quantum dots and quench their luminescence. Under these conditions, the reversible transformations of photochromic ligands or the irreversible cleavage of photocaged counterparts translates into the possibility to switch luminescence with external control. As an alternative to regulating the photophysics of a quantum dot via the photochemistry of its ligands, the photochemistry of the latter can be controlled by relying on the photophysics of the former. The transfer of excitation energy from a quantum dot to a photocaged ligand populates the excited state of the species adsorbed on the nanocrystal to induce a photochemical reaction. This mechanism, in conjunction with the large two-photon absorption cross section of quantum dots, can be exploited to release nitric oxide or to generate singlet oxygen under near-infrared irradiation. Thus, the combination of semiconductor quantum dots and photoresponsive ligands offers the opportunity to assemble nanostructured constructs with specific functions on the basis of electron or energy transfer processes. The photoswitchable luminescence and ability to photoinduce the release of reactive chemicals, associated with the resulting systems, can be particularly valuable in biomedical research and can, ultimately, lead to the realization of imaging probes for diagnostic applications as well as to therapeutic agents for the treatment of cancer.

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 (NQE) 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.

Saulite, L., et al. (2017). "Nano-engineered skin mesenchymal stem cells: potential vehicles for tumour-targeted quantum-dot delivery." Beilstein J Nanotechnol **8**: 1218-1230.

Nanotechnology-based drug design offers new possibilities for the use of nanoparticles in imaging and targeted therapy of tumours. Due to their tumour-homing ability, nano-engineered mesenchymal stem cells (MSCs) could be utilized as vectors to deliver diagnostic and therapeutic nanoparticles into a tumour. In the present study, uptake and functional effects of carboxyl-coated quantum dots QD655 were studied in human skin MSCs. The effect of QD on MSCs was examined using a cell viability assay, Ki67 expression analysis, and tri-lineage differentiation assay. The optimal conditions for QD uptake in MSCs were determined using flow cytometry. The QD uptake route in MSCs was examined via fluorescence imaging using endocytosis inhibitors for the micropinocytosis, phagocytosis, lipid-raft, clathrin- and caveolin-dependent endocytosis pathways. These data showed that QDs were efficiently accumulated in the cytoplasm of MSCs after incubation for 6 h. The main uptake route of QDs in skin MSCs was clathrin-mediated endocytosis. QDs were mainly localized in early endosomes after 6 h as well as in late endosomes and lysosomes after 24 h. QDs in concentrations ranging from 0.5 to 64 nM had no effect on cell viability and proliferation. The expression of MSC markers, CD73 and CD90, and hematopoietic markers, CD34 and CD45, as well as the ability to differentiate into adipocytes, chondrocytes, and osteocytes, were not altered in the presence of QDs. We observed a decrease

in the QD signal from labelled MSCs over time that could partly reflect QD excretion. Altogether, these data suggest that QD-labelled MSCs could be used for targeted drug delivery studies.

Semkova, S., et al. (2018). "Loading Efficiency of Polymersomes with Contrast Agents and their Intracellular Delivery: Quantum Dots Versus Organic Dyes." *Anticancer Res* **38**(2): 825-831.

**BACKGROUND/AIM:** Contrast nanocarriers as drug-delivery systems, capable of selective delivery to cancer cells and solid tumors, are essential for the development of new diagnostic and therapeutic (theranostic) strategies. The present study aimed to investigate the loading efficiency of chitosan-based polymersomes with fluorescent contrast substances [quantum dots (QDs) and conventional organic dyes] and the possibility to control their release from the polymer matrix into cells by chemical modifications and electroporation. **MATERIALS AND METHODS:** All investigated fluorophores were retained within the polymer globule via electrostatic and hydrophilic-hydrophobic interactions, without conjugation with the polymer. The fluorophore-loaded polymersomes were characterized by dynamic light scattering, zeta-potential titration, and fluorescence spectroscopy. The release of fluorophore from the polymersomes, passively or after electroporation, was detected by 5-step spin-ultrafiltration, combined with fluorescence spectroscopy of the upper phase (supernatant) of the filter unit. Passive intracellular delivery of the nanoparticles to HeLa cells was detected by fluorescence confocal microscopy. **RESULTS:** The QDs were retained tightly and continuously in the polymer matrix, while the organic fluorophores [fluorescein isothiocyanate (FITC), FITC-dextran(10,000) and FITC-dextran(70,000)] were released rapidly from the polymersomes. The detergent Brij significantly increased the retention of FITC-dextran(10,000) in the polymer globule. Electroporation up to 1000 V/cm did not induce release of QDs from the polymersomes, but accelerated the release of Brij-treated FITC-dextran(10,000) B from the polymer matrix. High-voltage pulses (over 750 V/cm) induced also fragmentation or aggregation of the nanoparticles. QD\_labeled polymersomes penetrated passively in cancer cells after 24-hour incubation. **CONCLUSION:** The results suggest that QD-labeled polymersomes are appropriate fluorescent probes and a nano-drug delivery system with high tracing opportunities for in vitro and in vivo applications. Furthermore, loading polymersomes with organic dyes with different molecular weights (such as FITC-dextrans) is a simple model for visualizing and predicting the rate of release of small organic

molecules (e.g. conventional drugs, other contrasts, stabilizers, and supplements) from the polymer matrix.

Shamirian, A., et al. (2016). "In vitro Detection of Hypoxia using a Ratiometric Quantum Dot-based Oxygen Sensor." *ACS Sens* **1**(10): 1244-1250.

A quantum-dot based ratiometric fluorescent oxygen probe for the detection of hypoxia in live cells is reported. The system is comprised of a water-soluble near-infrared emissive quantum dot conjugated to perylene dye. The response to the oxygen concentration is investigated using enzymatic oxygen scavenging in water, while in vitro studies were performed with HeLa cells incubated under varying O<sub>2</sub> levels. In both cases a significant enhancement in dye/QD emission intensity ratio was observed in the deoxygenated environment, demonstrating the possible use of this probe for cancer research.

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.

Su, X., et al. (2017). "A graphene quantum dot@Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> based nanoprobe for drug delivery sensing and dual-modal fluorescence and MRI imaging in cancer cells." *Biosens Bioelectron* **92**: 489-495.

A novel graphene quantum dot (GQD)@Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> based nanoprobe was reported for targeted drug delivery, sensing, dual-modal imaging and therapy. Carboxyl-terminated GQD (C-GQD) was firstly conjugated with Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> and then functionalized with cancer targeting molecule folic acid (FA). DOX drug molecules were then loaded on GQD surface of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@GQD-FA nanoprobe via pi-pi stacking, which resulted in Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@GQD-FA/DOX conjugates based on a FRET mechanism with GQD as donor molecules and DOX as acceptor molecules. Meanwhile, we successfully performed in vitro MRI and fluorescence imaging of living Hela cells and monitored intracellular drug release process using this Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@GQD-FA/DOX nanoprobe. Cell viability study demonstrated the low cytotoxicity of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@GQD-FA nanocarrier and the enhanced therapeutic efficacy of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>@GQD-FA/DOX nanoprobe for cancer cells. This luminomagnetic nanoprobe will be a potential platform for cancer accurate diagnosis and therapy.

Sun, G., et al. (2018). "Targeting breast cancer cells with a CuInS<sub>2</sub>/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 CuInS<sub>2</sub>/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 CuInS<sub>2</sub>/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, Z., et al. (2017). "TiL<sub>4</sub> -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.

Tang, J., et al. (2017). "Aptamer-conjugated PEGylated quantum dots targeting epidermal growth factor receptor variant III for fluorescence imaging of glioma." *Int J Nanomedicine* **12**: 3899-3911.

The extent of resection is a significant prognostic factor in glioma patients. However, the maximum safe resection level is difficult to determine due to the inherent infiltrative character of tumors. Recently, fluorescence-guided surgery has emerged as a new technique that allows safe resection of glioma. In this study, we constructed a new kind of quantum dot (QD)-labeled aptamer (QD-Apt) nanoprobe by conjugating aptamer 32 (A32) to the QDs surface, which can specially bind to the tumors. A32 is a single-stranded DNA capable of binding to the epidermal growth factor receptor variant III (EGFRvIII) specially distributed on the surface of glioma cells. To detect the expression of EGFRvIII in human brain tissues, 120 specimens, including 110 glioma tissues and 10 normal brain tissues, were examined by immunohistochemistry, and the results showed that the rate of positive expression of EGFRvIII in the glioma tissues was 41.82%, and 0.00% in normal brain tissues. Besides, the physiochemical properties of QD-Apt nanoparticles (NPs) were thoroughly characterized. Biocompatibility of the NPs was evaluated, and the results suggested that the QD-Apt was nontoxic in vivo and vitro. Furthermore, the use of the QD-Apt in labeling glioma cell lines and human brain glioma tissues, and target gliomas in situ was also investigated. We found that not only could QD-Apt specially bind to the U87-EGFRvIII glioma cells but also bind to human glioma tissues in vitro. Fluorescence imaging in vivo with orthotopic glioma model mice bearing U87-EGFRvIII showed that QD-Apt could penetrate the blood-brain barrier and then selectively accumulate in the tumors through binding to EGFRvIII, and consequently, generate a strong fluorescence, which contributed to the margins of gliomas that were visualized clearly, and thus, help the surgeons realize the maximum safe resection of glioma. In addition, QD-Apt can also be applied in preoperative diagnosis and postoperative examination of glioma. Therefore, these achievements facilitate the use of tumor-targeted fluorescence

imaging in the diagnosis, surgical resection, and postoperative examination of glioma.

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, MoS<sub>2</sub>, 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.

Tavares, A., et al. (2018). "Inhibition of the checkpoint protein PD-1 by the therapeutic antibody pembrolizumab outlined by quantum chemistry." *Sci Rep* **8**(1): 1840.

Much of the recent excitement in the cancer immunotherapy approach has been generated by the recognition that immune checkpoint proteins, like the receptor PD-1, can be blocked by antibody-based drugs with profound effects. Promising clinical data have already been released pointing to the efficiency of the drug pembrolizumab to block the PD-1 pathway, triggering the T-lymphocytes to destroy the cancer cells. Thus, a deep understanding of this drug/receptor complex is essential for the improvement of new drugs targeting the protein PD-1. In this context, by employing quantum chemistry methods based on the Density Functional Theory (DFT), we investigate in silico the binding energy features of the receptor PD-1 in complex with its drug inhibitor. Our computational results give a better understanding of the binding mechanisms, being also an efficient alternative towards the development of antibody-based drugs, pointing to new treatments for cancer therapy.

Tomic, S., et al. (2017). "Graphene quantum dots suppress proinflammatory T cell responses via

autophagy-dependent induction of tolerogenic dendritic cells." *Biomaterials* **146**: 13-28.

Graphene quantum dots (GQD) are atom-thick nanodimensional carbon sheets with excellent physico-chemical and biological properties, making them attractive for application in theranostics. However, their immunoregulatory properties are insufficiently investigated, especially in human primary immune cells. We found that non-toxic doses of GQD inhibit the production of proinflammatory and T helper (Th)1 cytokines, and augment the production of anti-inflammatory and Th2 cytokines by human peripheral blood mononuclear cells. While unable to affect T cells directly, GQD impaired the differentiation and functions of monocyte-derived dendritic cells (DC), lowering their capacity to stimulate T cell proliferation, development of Th1 and Th17 cells, and T-cell mediated cytotoxicity. Additionally, GQD-treated DC potentiated Th2 polarization, and induced suppressive CD4(+)CD25(high)Foxp3(+) regulatory T cells. After internalization in a dynamin-independent, cholesterol-dependent manner, GQD lowered the production of reactive oxygen species and nuclear translocation of NF-kappaB in DC. The activity of mammalian target of rapamycin (mTOR) was reduced by GQD, which correlated with the increase in transcription of autophagy genes and autophagic flux in DC. Genetic suppression of autophagy impaired the pro-tolerogenic effects of GQD on DC. Our results suggest that GQD-triggered autophagy promotes tolerogenic functions in monocyte-derived DC, which could be beneficial in inflammatory T-cell mediated pathologies, but also harmful in GQD-based anti-cancer therapy.

Tsuboi, S. and T. Jin (2017). "Bioluminescence Resonance Energy Transfer (BRET)-coupled Annexin V-functionalized Quantum Dots for Near-Infrared Optical Detection of Apoptotic Cells." *ChemBiochem* **18**(22): 2231-2235.

Deregulation in apoptosis induces numerous diseases such as cancer, cardiovascular, and neurodegenerative diseases. Detection of apoptotic cells is crucial for understanding the mechanism of these diseases and for therapy development. Although optical imaging using visible-emitting fluorescent probes, such as FITC-labeled annexin V, is widely used for the detection of apoptotic cells, there are very limited probes that can be used in the near-infrared region (NIR) over 700 nm. Compared with visible light, NIR light is highly permeable in turbid biological samples and tissues. In addition, optical imaging in the NIR region shows low autofluorescence from biological samples, leading to clearer images with high signal to background ratios. Here, we report the synthesis of bioluminescence resonance energy transfer (BRET)-coupled annexin V-functionalized quantum

dots (QDs) and their application to NIR optical detection of apoptotic cells.

Tsuboi, S. and T. Jin (2018). "Recombinant Protein (Luciferase-IgG Binding Domain) Conjugated Quantum Dots for BRET-Coupled Near-Infrared Imaging of Epidermal Growth Factor Receptors." Bioconjug Chem.

For the highly sensitive near-infrared (NIR) optical detection of epidermal growth factor receptors (EGFRs) expressed on cancer cells, bioluminescence resonance energy transfer (BRET) coupled NIR quantum dots (QDs) are prepared by direct conjugation of his-tagged Renilla luciferase (RLuc) recombinant protein (HisRLuc.GB1) to glutathione-coated CdSeTe/CdS QDs (GSH-QDs). The recombinant protein has two functional groups consisting of a luciferase enzyme and an immunoglobulin binding domain (GB1) of protein G. Recombinant protein (HisRLuc.GB1) conjugated QDs (GB1.RLuc-QDs) show BRET-coupled NIR emission, which results from energy transfer from luciferin to QDs with a high BRET efficiency of ca. 50%. Since the GB1.RLuc-QDs have the GB1 domain at their surface, the QDs have an ability to bind the Fc moiety of immunoglobulin G (IgG). The resulting IgG bound QDs can be used as a molecular imaging probe with NIR fluorescence and BRET-coupled NIR emission. For NIR optical detection of EGFRs on cancer cells, we conjugated anti-EGFR monoclonal antibody to the GB1.RLuc-QDs. Herein, we show that the detection sensitivity of EGFRs by BRET-coupled NIR emission of GB1.RLuc-QDs is at least three times higher than that of the NIR fluorescence of the QDs. The conjugates between anti-EGFR antibody and GB1.RLuc-QDs make it possible to perform BRET-based highly sensitive NIR imaging of EGFRs in living cells.

Tsuboi, S., et al. (2017). "Immunoglobulin binding (B1) domain mediated antibody conjugation to quantum dots for in vitro and in vivo molecular imaging." Chem Commun (Camb) **53**(68): 9450-9453.

A facile method for the preparation of antibody-quantum dot (QD) conjugates using the immunoglobulin binding (B1) domain of protein G is presented. The utility of antibody-QD conjugates using the B1 domain is demonstrated for fluorescence imaging of breast tumor cells in vitro and in vivo.

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.

Vibin, M., et al. (2017). "A Novel Fluorescent Quantum Dot Probe for the Rapid Diagnostic High Contrast Imaging of Tumor in Mice." J Fluoresc **27**(2): 669-677.

A simple probe - antibody conjugated silica over coated cadmium selenide quantum dots (QD-Ab probe) for efficient and rapid diagnostic in vivo imaging of tumors is developed. Compared to unconjugated quantum dots (QD), these probes underwent efficient cellular internalization and tumor targeting behavior, retaining bright emission under in vivo cancer models. Silica over coated cadmium selenide quantum dots were conjugated with Epidermal growth factor receptor (EGFR) monoclonal antibody to detect the over expression of EGFR in cancer models. The in vitro cellular internalization efficiency of QD and QD-Ab probe in cultured stem cells (RADMSCs) and cancer cells (HeLa) were assessed by ICP-OES and cLSM. Results demonstrated a greater internalization efficiency of CdSe-Silica QD-Ab probe than CdSe-Silica QDs. For in vivo imaging solid tumor bearing mice was subjected to tail vein injection of QD and QD-Ab probe. After the specific time interval of injection, mice were anesthetized and subjected into Xenogen IVIS(R)200 imaging system, followed by ex vivo imaging. Subsequently, ultrathin sections of tumor were imaged by using cLSM. Both in vivo and ex vivo imaging results confirmed the tumor-targeted imaging efficiency of QD-Ab probes compared to unconjugated QDs.

Wang, H., et al. (2017). "Photoelectrochemical immunosensor for methylated RNA detection based on g-C<sub>3</sub>N<sub>4</sub>/CdS quantum dots heterojunction and Phos-tag-biotin." Biosens Bioelectron **95**: 124-130.

N(6)-methyladenosine (m(6)A) is an enigmatic and abundant internal modification in eukaryotic messenger RNA (mRNA), which could affect various aspects of RNA metabolism and mRNA translation. Herein, a novel photoelectrochemical (PEC) immunosensor was constructed for m(6)A detection based on the inhibition of Cu(2+) to the photoactivity of g-C3N4/CdS quantum dots (g-C3N4/CdS) heterojunction, where g-C3N4/CdS heterojunction was used as photoactive material, anti-m(6)A antibody as recognition unit for m(6)A-containing RNA, Phos-tag-biotin as link unit and avidin functionalized CuO as PEC signal indicator. When CuO was captured on electrode through biotin-avidin affinity reaction and then treated with HCl, Cu(2+) could be released and CuxS would be formed based on the selective interaction between CdS and Cu(2+), leading the photocurrent obviously decreased. Under the optimal detection conditions, the PEC biosensor displayed a linear range of 0.01-10nM and a low detection limit of 3.53 pM for methylated RNA determination. Furthermore, the developed method could also be used to detect the expression level of m(6)A methylated RNA in serum samples of breast cancer patient before and after operative treatment. The proposed assay strategy has a great potential for detecting the expression methylation level of RNA in real sample.

Wang, J., et al. (2017). "Enhanced fluorescence of tetrasulfonated zinc phthalocyanine by graphene quantum dots and its application in molecular sensing/imaging." *Luminescence* **32**(4): 573-580.

When excited at 435 nm, tetra-sulfonate zinc phthalocyanine (ZnPcS4) emitted dual fluorescence at 495 and 702 nm. The abnormal fluorescence at 495 nm was experimentally studied and analyzed in detail for the first time. The abnormal fluorescence at 495 nm was deduced to originate from triplet-triplet (T-T) energy transfer of excited phthalocyanine ((3)\*ZnPcS4). Furthermore, graphene quantum dots (GQDs) enhanced the 495 nm fluorescence quantum yield (Q) of ZnPcS4. The fluorescence properties of ZnPcS4-GQDs conjugate were retained in a cellular environment. Based on the fluorescence of ZnPcS4-GQDs conjugate, we designed and prepared an Apt29/thrombin/Apt15 sandwich thrombin sensor with high specificity and affinity. This cost-saving, simple operational sensing strategy can be extended to use in sensing/imaging of other biomolecules.

Wang, L., et al. (2017). "Gram-Scale Synthesis of Hydrophilic PEI-Coated AgInS2 Quantum Dots and Its Application in Hydrogen Peroxide/Glucose Detection and Cell Imaging." *Inorg Chem* **56**(11): 6122-6130.

Assisted with polyethylenimine, 4.0 L of water-soluble AgInS2 quantum dots (AIS QDs) were

successfully synthesized in an electric pressure cooker. As-prepared QDs exhibit yellow emission with a photoluminescence (PL) quantum yield up to 32%. The QDs also show excellent water/buffer stability. The highly luminescent AIS QDs are used to explore their dual-functional behavior: detection of hydrogen peroxide (H2O2)/glucose and cell imaging. The amino-functionalized AIS QDs show high sensitivity and specificity for H2O2 and glucose with detection limits of 0.42 and 0.90 μM, respectively. A linear correlation was established between PL intensity and concentration of H2O2 in the ranges of 0.5-10 μM and 10-300 μM, while the linear ranges were 1-10 μM and 10-1000 μM for detection of glucose. The AIS QDs reveal negligible cytotoxicity on HeLa cells. Furthermore, the luminescence of AIS QDs gives the function of optical imaging.

Wang, L. J., et al. (2017). "Single quantum dot-based nanosensor for rapid and sensitive detection of terminal deoxynucleotidyl transferase." *Chem Commun (Camb)* **53**(80): 11016-11019.

We developed a simple and rapid method for terminal deoxynucleotidyl transferase (TdT) assay on the basis of the polymerization-directed exonuclease-assisted construction of a single quantum dot (QD)-based fluorescence resonance energy transfer (FRET) nanosensor. This method is very sensitive with a detection limit as low as  $1 \times 10^{-6}$  U μL<sup>-1</sup>, and it can be used for the screening of TdT inhibitors and accurate quantification of TdT activity even in 5 cancer cells.

Wang, S., et al. (2017). "Pattern Recognition of Cells via Multiplexed Imaging with Monosaccharide-Imprinted Quantum Dots." *Anal Chem* **89**(10): 5646-5652.

Recognition of cancer cells is essential for many important areas such as targeted cancer therapy. Multimonomosaccharide-based recognition could be a useful strategy to improve the recognition specificity, but such a possibility has not been explored yet. Herein we report pattern recognition of cells via multiplexed imaging with monosaccharide-imprinted quantum dots (QDs). Imprinted with sialic acid, fucose, and mannose as the template, respectively, the QDs exhibited good specificity toward the template monosaccharides. Multiplexed imaging of cells simultaneously stained with these monosaccharide-imprinted QDs revealed the relative expression levels of the monosaccharides on the cells. Pattern recognition constructed using the intensities of multiplexed imaging unveiled the similarities and differences of different cell lines, allowing for the recognition of not only cancer cells from normal cells but also cancer cells of different cell lines. Thus, this study paved a solid ground for the

design and preparation of novel cancer-cell targeting reagents and nanoprobe.

Wang, W., et al. (2017). "Ultraefficient Cap-Exchange Protocol To Compact Biofunctional Quantum Dots for Sensitive Ratiometric Biosensing and Cell Imaging." *ACS Appl Mater Interfaces* **9**(18): 15232-15244.

An ultraefficient cap-exchange protocol (UCEP) that can convert hydrophobic quantum dots (QDs) into stable, biocompatible, and aggregation-free water-dispersed ones at a ligand:QD molar ratio (LQMR) as low as 500, some 20-200-fold less than most literature methods, has been developed. The UCEP works conveniently with air-stable lipoic acid (LA)-based ligands by exploiting tris(2-carboxylethyl phosphine)-based rapid in situ reduction. The resulting QDs are compact (hydrodynamic radius,  $R_h$ , < 4.5 nm) and bright (retaining > 90% of original fluorescence), resist nonspecific adsorption of proteins, and display good stability in biological buffers even with high salt content (e.g., 2 M NaCl). These advantageous properties make them well suited for cellular imaging and ratiometric biosensing applications. The QDs prepared by UCEP using dihydrolipoic acid (DHLLA)-zwitterion ligand can be readily conjugated with octahistidine (His8)-tagged antibody mimetic proteins (known as Affimers). These QDs allow rapid, ratiometric detection of the Affimer target protein down to 10 pM via a QD-sensitized Förster resonance energy transfer (FRET) readout signal. Moreover, compact biotinylated QDs can be readily prepared by UCEP in a facile, one-step process. The resulting QDs have been further employed for ratiometric detection of protein, exemplified by neutravidin, down to 5 pM, as well as for fluorescence imaging of target cancer cells.

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-DESMIN-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.

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, Z., et al. (2018). "Antitumor effect of a Pt-loaded nanocomposite based on graphene quantum dots combats hypoxia-induced chemoresistance of oral squamous cell carcinoma." *Int J Nanomedicine* **13**: 1505-1524.

Background: Tumor microenvironment plays an important role in the chemoresistance of oral squamous cell carcinoma (OSCC). Hypoxia in the microenvironment is one of the important factors that contributes to OSCC chemoresistance; therefore overcoming hypoxia-mediated chemoresistance is one of the great challenges in clinical practice. Methods: In this study, we developed a drug delivery system based on Pt-loaded, polyethylene glycol-modified graphene quantum dots via chemical oxidation and covalent reaction. Results: Our results show that synthesized polyethylene glycol-graphene quantum dots-Pt (GPt) is

about 5 nm in diameter. GPt sensitizes OSCC cells to its treatment in both normoxia and hypoxia conditions. Inductively coupled plasma-mass spectrometry assay shows that GPt enhances Pt accumulation in cells, which leads to a notable increase of S phase cell cycle arrest and apoptosis of OSCC cells in both normoxia and hypoxic conditions. Finally, compared with free cisplatin, GPt exhibits a strong inhibitory effect on the tumor growth with less systemic drug toxicity in an OSCC xenograft mouse tumor model. Conclusion: Taken together, our results show that GPt demonstrates superiority in combating hypoxia-induced chemoresistance. It might serve as a novel strategy for future microenvironment-targeted cancer therapy.

Wu, F., et al. (2017). "Facile synthesis of N-rich carbon quantum dots from porphyrins as efficient probes for bioimaging and biosensing in living cells." *Int J Nanomedicine* **12**: 7375-7391.

N-rich metal-free and metal-doped carbon quantum dots (CQDs) have been prepared through one-step hydrothermal method using tetraphenylporphyrin or its transition metal (Pd or Pt) complex as precursor. The structures and morphology of the as-prepared nanoparticles were analyzed by X-ray diffraction, high-resolution transmission electron microscopy, X-ray photoelectron spectroscopy, and Fourier transform infrared spectra. Three kinds of nanocomposites show similar structures except for the presence of metal ions in Pd-CQDs and Pt-CQDs indicated by X-ray photoelectron spectroscopy. All of them display bright blue emission upon exposure to ultraviolet irradiation. The CQDs exhibit typical excitation-dependent emission behavior, with the emission quantum yield of 10.1%, 17.8%, and 15.2% for CQDs, Pd-CQDs, and Pt-CQDs, respectively. Moreover, the CQDs, Pd-CQDs, and Pt-CQDs could serve as fluorescent probes for the specific and sensitive detection of Fe(3+) ions in aqueous solution. The low cytotoxicity of CQDs is demonstrated by MTT assay against HeLa cells. Therefore, the CQDs can be used as efficient probes for cellular multicolor imaging and fluorescence sensors for the detection of Fe(3+) ions due to their low toxicity, excellent biocompatibility, and low detection limits. This work provides a new route to synthesize highly luminescent N-rich metal-free or metal-doped CQDs for multifunctional applications.

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.

Xiao, K., et al. (2017). "Use of quantum dot beads-labeled monoclonal antibody to improve the sensitivity of a quantitative and simultaneous immunochromatographic assay for neuron specific enolase and carcinoembryonic antigen." *Talanta* **164**: 463-469.

Detection of multiplex tumor markers was of great importance for cancer diagnosis. Immunochromatographic test strip (ICTS) was the most frequently-used point-of-care detection means. Herein, a convenient and fast method for simultaneous quantitative detection of neuron specific enolase (NSE) and carcinoembryonic antigen (CEA) was developed based on ICTS using quantum dot beads (QBs) as marking material. Good monodispersity, high colloidal stability and carboxyl-modified (COOH-) QBs were used. For this method, two test lines were applied to the NC membrane for simultaneous analysis of CEA and NSE respectively. The ideal limit of CEA and NSE detection was 0.0378ng/mL and 0.0426ng/mL with scarcely any cross-reactivity. Moreover, the fluorescent signal intensity of the nitrocellulose membrane could be easily read out in the cooperation of the "Handing" system without professional operators. The possible clinical utilization of this platform was demonstrated by detecting 100 clinic human serums. The result showed that the platform had sensitivity of 99% and 97% for CEA and NSE, while the specificity was 97% and 100% respectively. Our results indicated that the QBs based ICTS not only owning the ability of sensitive and specific simultaneous detection of CEA and NSE, but also showing the potential in developing this ICTS into a routine part of early lung cancer diagnosis.

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*.

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, 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 (H<sub>2</sub>O<sub>2</sub>) 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 H<sub>2</sub>O<sub>2</sub>, the resultant nanohybrid microelectrode exhibited good sensing performances for electrochemical detection of H<sub>2</sub>O<sub>2</sub>, including a high sensitivity of 371  $\mu\text{Acm}^{-2}$  mM<sup>-1</sup>, a wide linear range from 1.0  $\mu\text{M}$  to 18.44 mM, a low detection limit of 500 nM (a signal-to-noise ratio of 3:1), as well as good selectivity and biocompatibility, which could be used for real-time tracking H<sub>2</sub>O<sub>2</sub> released from different types of human breast cells and in situ sensitive detection of H<sub>2</sub>O<sub>2</sub> in clinical breast cancer tissue.

Xu, X., et al. (2017). "Selective recognition of cis-trans-isomers of platinum drugs and the detection of triplex DNA based on fluorescence reversible model of quantum dots." *J Pharm Biomed Anal* **134**: 94-99.

The identification of spatial structures of drugs and the researches on their interaction mechanism with DNA are always attractive to the researchers. However, their realization is lack of simple and fast method. This paper reports the establishment of multiple-functional detection platform based on the "turn off-on" model of ZnCdSe quantum dots. In this system, ZnCdSe quantum dots work as the fluorescent probe, platinum anti-cancer drugs as the quencher and triplex DNA as the trapping agent. The seemingly similar cisplatin and transplatin exhibited different fluorescent recovery behaviors due to their difference in structure, and thus realized the selective detection of cisplatin and transplatin with the reaction time set at 10 min as well as the quantitation of cisplatin over the range of  $2.5 \times 10^{-8}$ – $100 \times 10^{-8}$  M. Based on this, the interactions between platinum anti-cancer drugs and ctDNA as well as polymorphic DNA were further studied, and realized the recognition of triplex DNA. The multiple-functional detection platform integrates the functions of the filtration of high-efficient platinum anti-cancer drugs, the researches on interaction mechanism of drugs, and the recognition of polymorphic DNA, meaningful to the future treatment of viral and cancers based on antisense gene strategy.

Xu, Y., et al. (2018). "Recent progress in two-dimensional inorganic quantum dots." *Chem Soc Rev* **47**(2): 586-625.

The development of two-dimensional (2D) inorganic materials-based quantum dots (QDs) is still in its infancy but is triggering immense enthusiasm due to their high chemical stability, good aqueous dispersibility, excellent optical property, good biocompatibility and easy functionalization. This review covers almost all the extant 2D-QDs based on graphene, phosphorene, silicene, carbides, nitrides, transition metal dichalcogenide, transition metal oxides and MXenes, etc. Their categories, synthetic routes, properties, functionalization and applications are

critically highlighted. In the application section, special emphasis is placed on the progress in bioimaging, cancer therapy, fluorescent sensing and optoelectronics. Meanwhile, the latest advances in 2D QDs-based catalysis and energy since 2015 are addressed. Moreover, 2D nanoclusters, in particular 2D-QDs, are also included. This review provides guidance for 2D-QDs studies to meet the increasing demands in the many diverse applications.

Yang, B., et al. (2017). "Quantum Dots Labeling Strategy for "Counting and Visualization" of HepG2 Cells." *Anal Chem* **89**(3): 1879-1886.

We report a sensitive, selective, simple, and reliable magnetic immunoassay protocol for detection and imaging of HepG2 cells. After being captured by Cs-doped multicore magnetic nanoparticles (MMNPs), HepG2 cells were labeled by CdSe/ZnS quantum dots (QDs), which could be visualized by fluorescence imaging using the photoluminescence property of QDs, and subsequently, they can be counted by inductively coupled plasma mass spectrometry (ICP-MS) with Cd/Cs as elemental tag. Because of the superior photoluminescence properties and the large quantities of detectable Cd atoms contained in the QDs core, QDs play a dual function role in this assay, making the method easier and more comprehensive than other similar approaches. Under the optimal conditions, the limit of detection of 61 HepG2 cells and the relative standard deviation of 5.4% (800 HepG2 cells,  $n = 7$ ) were obtained. The linear range was 200-30000 cells, and the recoveries in human whole blood were in the range of 86-104%. The proposed method enables us not only to count but also to see the cancer cells with the same labeling process, opening a promising avenue for research and clinical application.

Yang, H. Y., et al. (2016). "Multifunctional Polymer Ligand Interface CdZnSeS/ZnS Quantum Dot/Cy3-Labeled Protein Pairs as Sensitive FRET Sensors." *ACS Appl Mater Interfaces* **8**(51): 35021-35032.

High-quality CdZnSeS/ZnS alloyed core/thick-shell quantum dots (QDs) as energy donors were first exploited in Forster resonance energy transfer (FRET) applications. A highly efficient ligand-exchange method was used to prepare low toxicity, high quantum yield, stabile, and biocompatible CdZnSeS/ZnS QDs densely capped with multifunctional polymer ligands containing dihydrolipoic acid (DHLLA). The resulting QDs can be applied to construct QDs-based Forster resonance energy transfer (FRET) systems by their high affinity interaction with dye cyanine 3 (Cy3)-labeled human serum albumin (HSA). This QD-based FRET protein complex can serve as a sensitive sensor for probing the interaction of clofazimine with proteins using

fluorescence spectroscopic techniques. The ability of FRET imaging both in vitro and in vivo not only reveals that the current FRET system can remain intact for 2 h but also confirms the potential of the FRET system to act as a nanocarrier for intracellular protein delivery or to serve as an imaging probe for cancer diagnosis.

Yang, J., et al. (2017). "Ultrasmall and photostable nanotheranostic agents based on carbon quantum dots passivated with polyamine-containing organosilane molecules." *Nanoscale* **9**(40): 15441-15452.

In this work, we demonstrate that ultrasmall, photostable and multifunctional carbon quantum dots (or carbon dots, CDs) passivated with polyamine-containing organosilane molecules can realize simultaneous cell imaging and anticancer drug delivery. The presence of abundant surface amine groups makes these CDs be able to covalently link with the anticancer drug, doxorubicin (DOX), with an extremely high drug loading capacity (62.8%), while the surface hydroxyl groups ensure the good water-dispersibility of the CDs-DOX. Besides the use as a drug carrier, the fluorescent CDs also enable the dynamic tracing of the drug release process. When the CDs-DOX complexes were internalized by the human breast cancer cells (MCF-7), DOX could gradually detach from the surface of CDs and enter into the cell nucleus, while the CDs themselves still resided in the cytoplasm. In addition, the in vivo experiments showed that the CDs-DOX complexes exhibited a better tumor inhibition performance than free DOX molecules, which may be ascribed to the prolonged drug accumulation in tumor tissues. Furthermore, the as-synthesized CDs also exhibited negligible cytotoxicity/systemic side effects, and could successfully illuminate mammalian, bacterial and fungal cells, making them good candidates as not only drug delivery vehicles but also universal cell imaging reagents. The present work may have implications for the fabrication of functional carbon-based nanomaterials and foster the development of carbon dots as novel nanotheranostics for various biomedical applications.

Yang, T., et al. (2017). "Surface-engineered quantum dots/electrospun nanofibers as a networked fluorescence aptasensing platform toward biomarkers." *Nanoscale* **9**(43): 17020-17028.

A membrane-based fluorescent sensing platform is a facile, point-of-care and promising technique in chemo/bio-analytical fields. However, the existing fluorescence sensing films for cancer biomarkers have several problems, with dissatisfactory sensitivity and selectivity, low utilization of probes encapsulated in films as well as the tedious design of membrane structures. In this work, a novel

fluorescence sensing platform is fabricated by bio-grafting quantum dots (QDs) onto the surface of electrospun nanofibers (NFs). The aptamer integrated into the QDs/NFs can result in high specificity for recognizing and capturing biomarkers. Partially complementary DNA-attached gold nanoparticles (AuNPs) are employed to efficiently hybridize with the remaining aptamer to quench the fluorescence of QDs by nanometal surface energy transfer (NSET) between them both, which are constructed for prostate specific antigen (PSA) assay. Taking advantage of the networked nanostructure of aptamer-QDs/NFs, the fluorescent film can detect PSA with high sensitivity and a detection limit of 0.46 pg mL<sup>-1</sup>, which was further applied in real clinical serum samples. Coupling the surface grafted techniques to the advanced network nanostructure of electrospun NFs, the proposed aptasensing platform can be easily extended to achieve sensitive and selective assays for other biomarkers.

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 CuInS<sub>2</sub>-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.

Yao, C., et al. (2017). "Tumor Cell-Specific Nuclear Targeting of Functionalized Graphene Quantum Dots In Vivo." *Bioconjug Chem* **28**(10): 2608-2619.

Specific targeting of tumor tissues is essential for tumor imaging and therapeutics but remains challenging. Here, we report an unprecedented method using synthetic sulfonic-graphene quantum dots (sulfonic-GQDs) to exactly target the cancer cell nuclei

in vivo without any bio- ligand modification, with no intervention in cells of normal tissues. The key factor for such selectivity is the high interstitial fluid pressure (IFP) in tumor tissues, which allows the penetration of sulfonic-GQDs into the plasma membrane of tumor cells. In vitro, the sulfonic-GQDs are repelled out of the cell membrane because of the repulsive force between negatively charged sulfonic-GQDs and the cell membranes which contributes to the low distribution in normal tissues in vivo. However, the plasma membrane-crossing process can be activated by incubating cells in ultrathin film culture medium because of the attachment of sulfonic-GQDs on cell membranes. Molecular dynamics simulations demonstrated that, once transported across the plasma membrane, the negatively charged functional groups of these GQDs will leave the membrane with a self-cleaning function retaining a small enough size to achieve penetration through the nuclear membrane into the nucleus. Our study showed that IFP is a previously unrecognized mechanism for specific targeting of tumor cell nuclei and suggested that sulfonic-GQDs may be developed into novel tools for tumor-specific imaging and therapeutics.

Yao, H., et al. (2016). "Construction of magnetic-carbon-quantum-dots-probe-labeled apoferritin nanocages for bioimaging and targeted therapy." *Int J Nanomedicine* **11**: 4423-4438.

Carbon dots (CDs) are one of the most highlighted carbon-based materials for biological applications, such as optical imaging nanoprobe, which are used for labeling cells in cancer treatment mainly due to their biocompatibility and unique optical properties. In this study, gadolinium (Gd)-complex-containing CDs were obtained through a one-step microwave method to develop multimodal nanoprobe integrating the advantages of optical and magnetic imaging. The obtained Gd-CDs exhibited highly fluorescent properties with excellent water solubility and biological compatibility. Natural apoferritin (AFn) nanocages, an excellent drug delivery carrier, are hollow in structure, with their pH-dependent, unfolding-refolding process at pH 2.0 and 7.4. The chemotherapeutic drug doxorubicin (DOX) can be highly effective and encapsulated into AFn cavity. A widely used tumor-targeting molecule, folic acid (FA), functionalized the surface of AFn to obtain an active tumor targeting effect on MCF-7 cells and malignant tumors in mice models. In this study, an AFn nanocarrier encapsulating high concentration of DOX labeled with magnetic and fluorescent Gd-CDs probe was developed. Gd-CDs exhibited a unique green photoluminescence and almost no toxicity compared with free GdCl<sub>3</sub>. Furthermore, Gd-doped CDs significantly increased the circulation time and

decreased the toxicity of Gd(3+) in in vitro and in vivo magnetic resonance imaging, which demonstrated that the AFn nanocages labeled with Gd-CD compounds could serve as an excellent T1 contrast agent for magnetic resonance imaging. The self-assembling multifunctional Gd-CDs/AFn (DOX)/FA nanoparticles have a great potential for cancer theranostic applications.

Yao, X., et al. (2017). "Graphene Quantum Dots-Capped Magnetic Mesoporous Silica Nanoparticles as a Multifunctional Platform for Controlled Drug Delivery, Magnetic Hyperthermia, and Photothermal Therapy." *Small* **13**(2).

A multifunctional platform is reported for synergistic therapy with controlled drug release, magnetic hyperthermia, and photothermal therapy, which is composed of graphene quantum dots (GQDs) as caps and local photothermal generators and magnetic mesoporous silica nanoparticles (MMSN) as drug carriers and magnetic thermoseeds. The structure, drug release behavior, magnetic hyperthermia capacity, photothermal effect, and synergistic therapeutic efficiency of the MMSN/GQDs nanoparticles are investigated. The results show that monodisperse MMSN/GQDs nanoparticles with the particle size of 100 nm can load doxorubicin (DOX) and trigger DOX release by low pH environment. Furthermore, the MMSN/GQDs nanoparticles can efficiently generate heat to the hyperthermia temperature under an alternating magnetic field or by near infrared irradiation. More importantly, breast cancer 4T1 cells as a model cellular system, the results indicate that compared with chemotherapy, magnetic hyperthermia or photothermal therapy alone, the combined chemo-magnetic hyperthermia therapy or chemo-photothermal therapy with the DOX-loaded MMSN/GQDs nanosystem exhibits a significant synergistic effect, resulting in a higher efficacy to kill cancer cells. Therefore, the MMSN/GQDs multifunctional platform has great potential in cancer therapy for enhancing the therapeutic efficiency.

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.

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.

Yu, F., et al. (2018). "Magnetic immunoassay using CdSe/ZnS quantum dots as fluorescent probes to detect the level of DNA methyltransferase 1 in human serum sample." Int J Nanomedicine **13**: 429-437.

Background: DNA methyltransferase 1 (DNMT1), a dominant enzyme responsible for the transfer of a methyl group from the universal methyl donor to the 5-position of cytosine residues in DNA, is essential for mammalian development and closely related to cancer and a variety of age-related chronic diseases. DNMT1 has become a useful biomarker in early disease diagnosis and a potential therapeutic target in cancer therapy and drug development. However, till now, most of the studies on DNA methyltransferase (MTase) detection have focused on the prokaryote MTase and its activity. Methods: A magnetic fluorescence-linked immunosorbent assay (FLISA) using CdSe/ZnS quantum dots as fluorescent probes was proposed for the rapid and sensitive detection of the DNMT1 level in this study. Key

factors that affect the precision and accuracy of the determination of DNMT1 were optimized. Results: Under the optimal conditions, the limit of detection was 0.1 ng/mL, the linear range was 0.1-1,500 ng/mL, the recovery was 91.67%-106.50%, and the relative standard deviations of intra- and inter-assays were respectively 5.45%-11.29% and 7.03%-11.25%. The cross-reactivity rates with DNA methyltransferases 3a and 3b were only 4.0% and 9.4%, respectively. Furthermore, FLISA was successfully used to detect the levels of DNMT1 in human serum samples, and compared with commercial enzyme-linked immunosorbent assay (ELISA) kits. The results revealed that there was a good correlation between FLISA and commercial ELISA kits (correlation coefficient  $r=0.866$ ,  $p=0.001$ ). The linear scope of FLISA was broader than ELISA, and the measurement time was much shorter than ELISA kits. Conclusion: These indicated that the proposed FLISA method was sensitive and high throughput and can quickly screen the level of DNMT1 in serum samples.

Yu, H. W., et al. (2017). "Preparation of quantum dots CdTe decorated graphene composite for sensitive detection of uric acid and dopamine." Anal Biochem **519**: 92-99.

The assembly of quantum dots (QDs) in a simply method opens up opportunities to obtain access to the full potential of assembled QDs by virtue of the collective properties of the ensembles. In this study, quantum dots CdTe and graphene (Gr) nanocomposite was constructed for the simultaneous determination of uric acid (UA) and dopamine (DA). The CdTe QDs-Gr nanocomposite was prepared by ultrasonication and was characterized with microscopic techniques. The nanocomposite modified electrode was characterized by cyclic voltammetry (CV), differential pulse voltammetry (DPV) and electrochemical impedance spectroscopy (EIS). Due to the synergistic effects between CdTe QDs and Gr, the fabricated electrode exhibited excellent electrochemical catalytic activities, good biological compatibility and high sensitivity toward the oxidation of UA and DA. Under optimum conditions, in the co-existence system the linear calibration plots for UA and DA were obtained over the range of 3-600  $\mu\text{M}$  and 1-500  $\mu\text{M}$  with detection limits of 1.0  $\mu\text{M}$  and 0.33  $\mu\text{M}$ . The fabricated biosensor also exhibits the excellent repeatability, reproducibility, storage stability along with acceptable selectivity.

Yu, X., et al. (2017). "Fluorine-free preparation of titanium carbide MXene quantum dots with high near-infrared photothermal performances for cancer therapy." Nanoscale **9**(45): 17859-17864.

Titanium carbide MXene quantum dots (QDs) were synthesized using an effective fluorine-free method as a biocompatible and highly efficient nanoagent for photothermal therapy (PTT) applications. In contrast to the traditional, hazardous and time-consuming process of HF pretreatment, our fluorine-free method is safe and simple. More importantly, abundant Al oxoanions were found to be modified on the MXene QD surface by the fluorine-free method, which endowed the QDs with strong and broad absorption in the NIR region. As a result, the as-prepared MXene QDs exhibited an extinction coefficient as large as  $52.8 \text{ Lg}(-1) \text{ cm}(-1)$  at 808 nm and a photothermal conversion efficiency as high as 52.2%. Both the values are among the best reported so far. The as-prepared MXene QDs achieved simultaneous photoacoustic (PA) imaging and the remarkable PTT effect of tumors. Moreover, MXene QDs showed great biocompatibility without causing noticeable toxicity in vitro and in vivo, indicating their high potential for clinical applications.

Yu, Z., et al. (2018). "Effects of TiO<sub>2</sub>, SiO<sub>2</sub>, Ag and CdTe/CdS quantum dots nanoparticles on toxicity of cadmium towards *Chlamydomonas reinhardtii*." *Ecotoxicol Environ Saf* **156**: 75-86.

Nanoparticles (NPs) are inevitably released into the aquatic environment for being widely used and may affect the toxicity of other contaminants already present in the environment, such as trace metals. However, the effects of NPs on the ecotoxicity of cadmium (Cd), a common environmental trace metal pollutant, are not well explored. In this study, effects of four widely used NPs TiO<sub>2</sub> (n-TiO<sub>2</sub>), SiO<sub>2</sub> (n-SiO<sub>2</sub>), Ag (n-Ag) and CdTe/CdS core/shell quantum dots (QD) on the toxicity of Cd to the freshwater algae *Chlamydomonas reinhardtii* were assessed respectively. Cd reduced the algae biomass, impaired the photosynthetic activities, and led to intracellular oxidative stress of algae. At non-toxic concentrations, both n-TiO<sub>2</sub> (100mgL<sup>-1</sup>) and n-SiO<sub>2</sub> (400mgL<sup>-1</sup>) attenuated the toxicity of Cd towards the algae for reducing the intracellular Cd contents, and the former was more pronounced. QD (0.5mgL<sup>-1</sup>) increased the toxicity of Cd to algae, but n-Ag (0.2mgL<sup>-1</sup>) had no significant influence on the Cd toxicity to algae. The microscopic observations on the ultrastructure of algae cells presented the same phenomena and n-TiO<sub>2</sub>, n-SiO<sub>2</sub> aggregations were clearly observed outside the cell wall. Furthermore, the regulation of NPs to the Cd toxicity towards algae was related to the intracellular nitric oxide (NO), an important signaling molecule, rather than the phototaxis of algae. Above all, this study provided a basic understanding about the difference in joint toxicity of different kinds of NPs and Cd to aquatic organisms.

Zalgeviciene, V., et al. (2017). "Quantum dots mediated embryotoxicity via placental damage." *Reprod Toxicol* **73**: 222-231.

The increasing use of nanoparticles in consumer products raises the concerns of their safety. This study investigated the biological effects of quantum dots (QD) exposure to rats during pregnancy. CdTe QD were injected on the 13th gestation day. Morphological features of 121 fetuses and histological analysis of placentas were performed on the 20th gestation day. The results showed that QD exhibit dose dependent embryotoxicity: survival rates of fetuses were 97% (5mg/kg dose), 86% (10mg/kg dose) and 43% (20mg/kg dose). QD exposure also resulted in the reduction of fetal body length and mass, disturbed ossification of limbs and caused placental tissue damage. QD exhibit no teratogenic effects at the applied doses. It is hypothesized that embryogenesis was impeded due to the placental damage rather than QD penetration and accumulation in the fetuses. To conclude, mothers should be protected from QD exposure during pregnancy.

Zavari-Nematabad, A., et al. (2017). "Development of quantum-dot-encapsulated liposome-based optical nanobiosensor for detection of telomerase activity without target amplification." *Anal Bioanal Chem* **409**(5): 1301-1310.

Reactivation of telomerase, which is observed in more than 85% of all known human tumours, is considered a promising tumour marker for cancer diagnosis. With respect to the biomedical importance of telomerase, we have developed a simple strategy based on liposomal fluorescent signal amplification for highly sensitive optical detection of telomerase activity using liposome-encapsulated cadmium telluride quantum dots. In this strategy, telomerase extracted from A549 cells elongated the biotinylated telomerase substrate primer, which was then immobilized on streptavidine-coated microplate wells. After the hybridization of the telomerase-elongated product with biotinylated capture probe, streptavidin was added to the assembly. In the next step, biotinylated liposome was conjugated with capture probe through streptavidin. Finally, QD-encapsulated liposomes were disrupted by Triton X-100, and the fluorescence intensity of the released QDs was measured to detect telomerase activity. The results showed that the proposed nanobiosensor was able to detect telomerase activity from as few as 10 A549 cells without the enzymatic amplification of telomerase extension products. In short, this method is not only convenient and sensitive, but also has a simple operating protocol and a wide detection range (10-5000 cells). A linear range was observed between 50 and 800 cells with a correlation

coefficient of 0.982 and regression equation of  $y = 0.0444x + 17.137$ . The proposed method is economical, more user-friendly, without error-prone PCR, with a wide detection range and simple operating protocol without the requirement for sophisticated equipment. Graphical Abstract Schematic representation of the QD-encapsulated liposome-based strategy to amplify fluorescence signal for optical detection of telomerase activity.

Zhang, D., et al. (2018). "Mitochondrial specific photodynamic therapy by rare-earth nanoparticles mediated near-infrared graphene quantum dots." *Biomaterials* **153**: 14-26.

Photodynamic therapy (PDT) has been proposed in cancer treatment for decades, but its clinical translation is significantly impeded by the low yield of ROS, poor tissue penetration depth of most current photosensitizers, and short lifetime of ROS. These limitations directly affect the therapeutic effect of PDT in cancer therapy. Here we proposed a new strategy by collaboratively integrating rare-earth doped upconversion nanoparticles (UCNP) with graphene quantum dot (GQD) for highly efficacious PDT, based on the merits of UCNP, which can emit UV-vis light under near-infrared light (NIR) excitation, and GQD, which can produce  $(1)O_2$  efficiently. For GQD-decorated UCNP nanoparticles (UCNP-GQD), the emission light from UCNP can further excite GQD with prominent  $(1)O_2$  generation for NIR-triggered PDT. Furthermore, a hydrophilic rhodamine derivative, TRITC, is covalently tethered to afford the resultant UCNP-GQD/TRITC, possessing distinct mitochondrial targeting property. Thus mitochondrial specific PDT with in-situ  $(1)O_2$  burst in mitochondria induces sharp decrease of mitochondrial membrane potential, which initiates the tumor cell apoptosis irreversibly. Importantly, in vivo experiments demonstrate the tumor inhibition of mitochondrial targeting UCNP-GQD/TRITC with improved therapeutic efficiency compared with non-targeting UCNP-GQD. The proposed strategy highlights the advantages of precision organelles-specific PDT in cancer therapy.

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, L., et al. (2017). "Multifunctional quantum dot DNA hydrogels." *Nat Commun* **8**(1): 381.

Biotemplated nanomaterials offer versatile functionality for multimodal imaging, biosensing, and drug delivery. There remains an unmet need for traceable and biocompatible nanomaterials that can be synthesized in a precisely controllable manner. Here, we report self-assembled quantum dot DNA hydrogels that exhibit both size and spectral tunability. We successfully incorporate DNA-templated quantum dots with high quantum yield, long-term photostability, and low cytotoxicity into a hydrogel network in a single step. By leveraging DNA-guided interactions, we introduce multifunctionality for a variety of applications, including enzyme-responsive drug delivery and cell-specific targeting. We report that quantum dot DNA hydrogels can be used for delivery of doxorubicin, an anticancer drug, to increase potency 9-fold against cancer cells. This approach also demonstrated high biocompatibility, trackability, and in vivo therapeutic efficacy in mice bearing xenografted breast cancer tumors. This work paves the way for the development of new tunable biotemplated nanomaterials with multiple synergistic functionalities for biomedical applications. The development of nanomaterials for imaging and drug delivery has been of great interest to the field. Here, the authors synthesized multifunctional enzyme-responsive hydrogels with self-assembling quantum dots for nucleic acid and drug delivery as well as having imaging capability.

Zhao, M. X., et al. (2018). "The delivery of doxorubicin of multifunctional beta-cyclodextrin-modified CdSe/ZnS quantum dots for bioactivity and nano-probing." *Chem Biol Drug Des* **91**(1): 285-293.

The modified quantum dots (QDs) have been used in intracellular probing and drug delivery because of their special chemical and physical properties. In this paper, two beta-cyclodextrin (beta-CD)-modified CdSe/ZnS QDs with strong optical emission properties were synthesized as drug carriers to induce apoptosis. The positively charged L-Arginine (L-Arg) and neutral L-Tryptophan (L-Trp) were selected as ligands to compare the effect of charge on bioactivity of QDs nanoparticles. The in vitro assays revealed that these modified QDs showed good Dox carrier ability and significantly high inhibition rate to cancer cells. Especially, the more positively charged beta-CD-L-Arg-polyamine-coated CdSe/ZnS QDs could effectively deliver the doxorubicin (Dox) into cells and exhibit excellent cell selectivity in cancer versus normal cells. The Dox-loaded QDs could enter intracellular, which showed that the Dox can efficiently go through the membranes at the existence of beta-CD. Several lines of evidence suggest that the Dox-loaded QDs can efficiently induce apoptosis likely related to the production of ROS. We expect that the modified QDs can enhance the amount of hydrophobic antitumor drugs in cells and can also be used as fluorescent imaging agents.

Zhao, Y., et al. (2017). "Near-Infrared Quantum Dot and (89)Zr Dual-Labeled Nanoparticles for in Vivo Cerenkov Imaging." *Bioconjug Chem* **28**(2): 600-608.

Cerenkov luminescence (CL) is an emerging imaging modality that utilizes the light generated during the radioactive decay of many clinical used isotopes. Although it is increasingly used for background-free imaging and deep tissue photodynamic therapy, in vivo applications of CL suffer from limited tissue penetration. Here, we propose to use quantum dots (QDs) as spectral converters that can transfer the CL UV-blue emissions to near-infrared light that is less scattered or absorbed in vivo. Experiments on tissue phantoms showed enhanced penetration depth and increased transmitted intensity for CL in the presence of near-infrared (NIR) QDs. To realize this concept for in vivo imaging applications, we developed three types of NIR QDs and (89)Zr dual-labeled nanoparticles based on lipid micelles, nanoemulsions, and polymeric nanoplateforms, which enable codelivery of the radionuclide and the QDs for maximized spectral conversion efficiency. We finally demonstrated the application of these self-illuminating nanoparticles for imaging of lymph nodes and tumors in a prostate cancer mouse model.

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, W., et al. (2018). "Acute and chronic cadmium telluride quantum dots-exposed human bronchial epithelial cells: The effects of particle sizes on their cytotoxicity and carcinogenicity." *Biochem Biophys Res Commun* **495**(1): 899-903.

Quantum dots (QDs) are semiconducting nanocrystals with unique optical properties. When coated with shell/capping, QDs are not deleterious to cells and organisms. However, when QDs are retained in the cellular environment for a certain period of time, their coatings may be degraded, yielding "naked" QDs.



Although some studies have documented the acute effects of cadmium telluride (CdTe) QDs in various cell lines, however, to our knowledge, there are no published studies on the chronic effects of CdTe QDs in normal lung cells. In this study, we therefore sought to study the effects of CdTe QDs of various particle sizes on their cytotoxicity and carcinogenicity in normal human bronchial epithelial cells (BEAS-2B). A total of three particle sizes of CdTe QD with emission maximum at 520, 580, and 730 nm were employed (abbreviated as 520Q, 580Q, and 730Q, respectively). Our results indicated that acute exposure to 520Q (approximately 2.04 nm in diameter) and 580Q (approximately 3.24 nm in diameter) elicited dose-dependent cytotoxicity; while acute exposure to 730Q (approximately 5.40 nm in diameter) elicited negligible cytotoxicity in BEAS-2B cells. Notably, chronic exposure to CdTe QD of all three tested particle sizes induced BEAS-2B cell transformation as evidenced by enhanced cell migration and anchorage-independent growth on soft agar. Taken together, our findings suggest that CdTe QDs are potent human lung carcinogens.

Zhou, Y., et al. (2016). "Daunorubicin and gambogic acid coloaded cysteamine-CdTe quantum dots minimizing the multidrug resistance of lymphoma in vitro and in vivo." *Int J Nanomedicine* **11**: 5429-5442.

To minimize the side effects and the multidrug resistance (MDR) arising from daunorubicin (DNR) treatment of malignant lymphoma, a chemotherapy formulation of cysteamine-modified cadmium tellurium (Cys-CdTe) quantum dots coloaded with DNR and gambogic acid (GA) nanoparticles (DNR-GA-Cys-CdTe NPs) was developed. The physical property, drug-loading efficiency and drug release behavior of these DNR-GA-Cys-CdTe NPs were evaluated, and their cytotoxicity was explored by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide assay. These DNR-GA-Cys-CdTe NPs possessed a pH-responsive behavior, and displayed a dose-dependent antiproliferative activity on multidrug-resistant lymphoma Raji/DNR cells. The accumulation of DNR inside the cells, revealed by flow cytometry assay, and the down-regulated expression of P-glycoprotein inside the Raji/DNR cells measured by Western blotting assay indicated that these DNR-GA-Cys-CdTe NPs could minimize the MDR of Raji/DNR cells. This multidrug delivery system would be a promising strategy for minimizing MDR against the lymphoma.

Zou, Y., et al. (2017). "Systematic study of imidazoles inhibiting IDO1 via the integration of molecular mechanics and quantum mechanics calculations." *Eur J Med Chem* **131**: 152-170.

Indoleamine 2,3-dioxygenase 1 (IDO1) is regarded as an attractive target for cancer immunotherapy. To rationalize the detailed interactions between IDO1 and its inhibitors at the atomic level, an integrated computational approach by combining molecular mechanics and quantum mechanics methods was employed in this report. Specifically, the binding modes of 20 inhibitors was initially investigated using the induced fit docking (IFD) protocol, which outperformed other two docking protocols in terms of correctly predicting ligand conformations. Secondly, molecular dynamics (MD) simulations and MM/PBSA free energy calculations were employed to determine the dynamic binding process and crucial residues were confirmed through close contact analysis, hydrogen-bond analysis and binding free energy decomposition calculations. Subsequent quantum mechanics and nonbonding interaction analysis were carried out to provide in-depth explanations on the critical role of those key residues, and Arg231 and 7-propionate of the heme group were major contributors to ligand binding, which lowered a great amount of interaction energy. We anticipate that these findings will be valuable for enzymatic studies and rational drug design.

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