

## Cancer and Quantum 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. In physics, a quantum is the minimum amount of any physical entity involved in an interaction. The fundamental notion that a physical property may be "quantized" is referred to as "the hypothesis of quantization". This means that the magnitude of the physical property can take on only discrete values consisting of integer multiples of one quantum. For example, a photon is a single quantum of light (or of any other form of electromagnetic radiation), and can be referred to as a "light quantum". Similarly, the energy of an electron bound within an atom is also quantized, and thus can only exist in certain discrete values. Atoms and matter in general are stable because electrons can only exist at discrete energy levels in an atom. Quantization is one of the foundations of the much broader physics of quantum mechanics. Quantization of the energy and its influence on how energy and matter interact (quantum electrodynamics) is part of the fundamental framework for understanding and describing nature. This article introduces recent research reports as references in the related studies.

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

### 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. In physics, a quantum is the minimum amount of any physical entity involved in an interaction. The fundamental notion that a physical property may be "quantized" is referred to as "the hypothesis of quantization". This means that the magnitude of the physical property can take on only discrete values consisting of integer multiples of one quantum. For example, a photon is a single quantum of light (or of any other form of electromagnetic radiation), and can be referred to as a "light quantum". Similarly, the energy of an electron bound within an atom is also quantized, and thus can only exist in certain discrete values. Atoms and matter in general are stable because electrons can only exist at discrete energy levels in an atom. Quantization is one of the foundations of the much broader physics of quantum mechanics. Quantization of the energy and its influence on how energy and matter interact (quantum

electrodynamics) is part of the fundamental framework for understanding and describing nature. 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 electro-conductivity 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<sup>-1</sup> (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.

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.

Ding, D., et al. (2017). "MoO<sub>3</sub>-x quantum dots for photoacoustic imaging guided photothermal/photodynamic cancer treatment." *Nanoscale* **9**(5): 2020-2029.

A theranostic system of image-guided phototherapy is considered as a potential technique for cancer treatment because of the ability to integrate diagnostics and therapies together, thus enhancing accuracy and visualization during the treatment. In this work, we realized photoacoustic (PA) imaging-guided photothermal (PT)/photodynamic (PD) combined cancer treatment just via a single material, MoO<sub>3</sub>-x quantum dots (QDs). Due to their strong NIR harvesting ability, MoO<sub>3</sub>-x QDs can convert incident light into hyperthermia and sensitize the formation of singlet oxygen synchronously as evidenced by in vitro assay, hence, they can behave as both PT and PD agents effectively and act as a "dual-punch" to cancer cells. In a further study, elimination of solid tumors from HeLa-tumor bearing mice could be achieved in a MoO<sub>3</sub>-x QD mediated phototherapeutic group without obvious lesions to the major organs. In addition, the desired PT effect also makes MoO<sub>3</sub>-x QDs an exogenous PA contrast agent for in vivo live-imaging to depict tumors. Compared with previously reported theranostic systems that put several components into one system, our multifunctional agent of MoO<sub>3</sub>-x QDs is exempt from unpredictable mutual interference between components and ease of leakage of virtual components from the composited system.

Ding, H., et al. (2017). "Beyond a Carrier: Graphene Quantum Dots as a Probe for Programmatically Monitoring Anti-Cancer Drug

Delivery, Release, and Response." *ACS Appl Mater Interfaces* **9**(33): 27396-27401.

On the basis of the unique physicochemical properties of graphene quantum dots (GQDs), we developed a novel type of theranostic agent by loading anticancer drug doxorubicin (DOX) to GQD's surface and conjugating Cy5.5 (Cy) dye to GQD through 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 (Ms) 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.

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 (DHLLA) ligands resulting in nanocrystals with high water-stability having an intense phosphorescent signal. Covalent bioconjugation of the DHLLA-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.

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 metabolism 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 HaCaT 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<sup>-1</sup>, and the limit of SOD2 detection equal to 0.44 ng mL<sup>-1</sup> (1.96 x 10<sup>-11</sup> 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.

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 polycysteine/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).

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.

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

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

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. QDs 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 upto 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<sup>-1</sup>mM<sup>-1</sup>), 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 facial 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.

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<sub>el</sub>) 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 CMC<sub>el</sub> shell. Moreover, CMC<sub>el</sub> 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 nanoplatfoms 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 because it is one of the leading causes of death 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 costained 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 3x10<sup>5</sup> 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 µg/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<sup>+</sup> Foxp3<sup>+</sup> 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 brought 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 28microUmL (-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.

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

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-Coadsorbed Carbon Quantum Dots Electrochemiluminescence Probe for the Evaluation of CD44 Expression on Breast Cancer Cells." *ACS Appl Mater Interfaces* **9**(20): 16848-16856.

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

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 probe 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 (NQEs) strengthen both the strong and the weak H bonds. This is in contrast to what is

observed for the cases where the proton affinity of the donors and acceptors is same. These structural fluctuations cause a significant red-shift in the absorption spectra and an increase in the broadening, bringing it into closer agreement with the experiments. Our work shows that nuclear quantum effects alter both qualitatively and quantitatively the optical properties of this biologically relevant system and highlights the importance of the inclusion of these effects in the microscopic understanding of their optical properties. We propose that isotopic substitution will produce a blue shift and a reduction in the broadening of the absorption peak.

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-dextran) 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.

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 epimetalomes 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.

Yang, J., et al. (2017). "Ultrascale 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 ultrascale, 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.

Zalgevičienė, 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<sub>2</sub> efficiently. For GQD-decorated UCNP nanoparticles (UCNP-GQD), the emission light from UCNP can further excite GQD with prominent (1)O<sub>2</sub> 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<sub>2</sub> 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.

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## References

1. 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.

2. Antaris, A. L., et al. (2017). "A high quantum yield molecule-protein complex fluorophore for near-infrared II imaging." *Nat Commun* 8: 15269.
3. 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.
4. 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.
5. Baidu. <http://www.baidu.com>. 2018.
6. 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.
7. 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.
8. 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*.
9. 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.
10. 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.
11. Borghei, 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.
12. Boriachek, K., et al. (2017). "Quantum dot-based sensitive detection of disease specific exosome in serum." *Analyst* 142(12): 2211-2219.
13. Dapkute, D., et al. (2017). "Skin-derived mesenchymal stem cells as quantum dot vehicles to tumors." *Int J Nanomedicine* 12: 8129-8142.
14. 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.
15. 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.
16. Ding, D., et al. (2017). "MoO<sub>3</sub>-x quantum dots for photoacoustic imaging guided photothermal/photodynamic cancer treatment." *Nanoscale* 9(5): 2020-2029.
17. 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.
18. 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.
19. Elakkiya, V., et al. (2017). "Optical detection of CA 15.3 breast cancer antigen using CdS quantum dot." *IET Nanobiotechnol* 11(3): 268-276.
20. 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.
21. 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.
22. Google. <http://www.google.com>. 2018.
23. 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 HaCaT cells." *Mikrochim Acta* 185(2): 128.
24. 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.
25. Hasanazadeh, 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.
26. Hasanazadeh, 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*.
27. Hasanazadeh, 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.
28. 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.
29. Iannazzo, D., et al. (2017). "Graphene quantum dots for cancer targeted drug delivery." *Int J Pharm* 518(1-2): 185-192.
30. Iliyasa, 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).
31. 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.
32. 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.
33. 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.
34. Jeong, S., et al. (2017). "Cancer-Microenvironment-Sensitive Activatable Quantum Dot Probe in the Second Near-Infrared Window." *Nano Lett* 17(3): 1378-1386.
35. Jha, S., et al. (2017). "Pharmaceutical potential of quantum dots." *Artif Cells Nanomed Biotechnol*: 1-9.
36. 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.
37. 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.
38. 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.
39. Kim, J. H., et al. (2017). "Anticancer luminescent gold quantum clusters for in situ cancer-selective marking-imaging-targeting." *Nanoscale* 9(26): 9071-9082.



40. 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.
41. 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.
42. Kominkova, M., et al. (2017). "Comparative study on toxicity of extracellularly biosynthesized and laboratory synthesized CdTe quantum dots." *J Biotechnol* 241: 193-200.
43. 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.
44. 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.
45. Lee, H., et al. (2017). "Optical coding of fusion genes using multicolor quantum dots for prostate cancer diagnosis." *Int J Nanomedicine* 12: 4397-4407.
46. Ma H, Chen G. Stem cell. The Journal of American Science 2005;1(2):90-92.
47. Ma H, Cherg S. Eternal Life and Stem Cell. Nature and Science. 2007;5(1):81-96.
48. Ma H, Cherg S. Nature of Life. Life Science Journal 2005;2(1):7-15.
49. Ma H, Yang Y. Turritopsis nutricula. Nature and Science 2010;8(2):15-20.  
[http://www.sciencepub.net/nature/ns0802/03\\_1279\\_hongbao\\_turritopsis\\_ns0802\\_15\\_20.pdf](http://www.sciencepub.net/nature/ns0802/03_1279_hongbao_turritopsis_ns0802_15_20.pdf).
50. Ma H. The Nature of Time and Space. Nature and science 2003;1(1):1-11. Nature and science 2007;5(1):81-96.
51. 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.
52. 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.
53. 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.
54. Manshian, B. B., et al. (2017). "Personalized medicine and follow-up of therapeutic delivery through exploitation of quantum dot toxicity." *Biomaterials* 127: 1-12.
55. 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.
56. 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.
57. Mansur, A. A., et al. (2017). "Carboxymethylcellulose/ZnCdS fluorescent quantum dot nanoconjugates for cancer cell bioimaging." *Int J Biol Macromol* 96: 675-686.
58. Mareeswari, P., et al. (2016). "Rhizopus stolonifer mediated biosynthesis of biocompatible cadmium chalcogenide quantum dots." *Enzyme Microb Technol* 95: 225-229.
59. Marsland Press. <http://www.sciencepub.net>. 2018.
60. McHugh, K. J., et al. (2018). "Biocompatible Semiconductor Quantum Dots as Cancer Imaging Agents." *Adv Mater*.
61. 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.
62. 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.
63. 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.
64. 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.
65. 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.
66. 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.
67. 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.
68. 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.
69. Naderi, S., et al. (2018). "Cadmium telluride quantum dots induce apoptosis in human breast cancer cell lines." *Toxicol Ind Health*: 748233718763517.
70. 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.
71. Namdari, P., et al. (2017). "Synthesis, properties and biomedical applications of carbon-based quantum dots: An updated review." *Biomed Pharmacother* 87: 209-222.
72. 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.
73. National Center for Biotechnology Information, U.S. National Library of Medicine. <http://www.ncbi.nlm.nih.gov/pubmed>. 2018.
74. 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.
75. 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.
76. 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.
77. 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.
78. 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.
79. Parani, S., et al. (2018). "Gelatin stabilization of quantum dots for improved stability and biocompatibility." *Int J Biol Macromol* 107(Pt A): 635-641.
80. Pardo, J., et al. (2018). "Cancer Targeting and Drug Delivery Using Carbon-Based Quantum Dots and Nanotubes." *Molecules* 23(2).
81. Pati, M. L., et al. (2018). "Quantum Dot Based Luminescent Nanoprobes for Sigma-2 Receptor Imaging." *Mol Pharm* 15(2): 458-471.
82. Peynshaert, K., et al. (2017). "Coating of Quantum Dots strongly defines their effect on lysosomal health and autophagy." *Acta Biomater* 48: 195-205.
83. 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.
84. 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.
  85. Pohanka, M. (2017). "Quantum Dots in the Therapy: Current Trends and Perspectives." *Mini Rev Med Chem* 17(8): 650-656.
  86. Qiu, Y., et al. (2017). "Novel Single-Cell Analysis Platform Based on a Solid-State Zinc-Coadsorbed Carbon Quantum Dots Electrochemiluminescence Probe for the Evaluation of CD44 Expression on Breast Cancer Cells." *ACS Appl Mater Interfaces* 9(20): 16848-16856.
  87. 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.
  88. 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.
  89. 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.
  90. Rodzik, L., et al. (2017). "Novel fluorescent CdTe quantum dot-thymine conjugate-synthesis, properties and possible application." *Nanotechnology* 28(4): 045701.
  91. 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.
  92. Sansalone, L., et al. (2016). "Semiconductor Quantum Dots with Photoresponsive Ligands." *Top Curr Chem (Cham)* 374(5): 73.
  93. Sappati, S., et al. (2016). "Nuclear quantum effects in a HIV/cancer inhibitor: The case of ellipticine." *J Chem Phys* 145(20): 205102.
  94. 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.
  95. 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.
  96. Shamirian, A., et al. (2016). "In vitro Detection of Hypoxia using a Ratiometric Quantum Dot-based Oxygen Sensor." *ACS Sens* 1(10): 1244-1250.
  97. 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.
  98. 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.
  99. 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.
  100. 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*.
  101. 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.
  102. Uthamacumar, A. (2017). "A biophysical approach to cancer dynamics: Quantum chaos and energy turbulence." *Biosystems* 156-157: 1-22.
  103. Wikipedia. Quantum. <https://en.wikipedia.org/wiki/Quantum>. 2018.
  104. Wikipedia. The free encyclopedia. <http://en.wikipedia.org>. 2018.
  105. Yang, J., et al. (2017). "Ultrascale and photostable nanotheranostic agents based on carbon quantum dots passivated with polyamine-containing organosilane molecules." *Nanoscale* 9(40): 15441-15452.
  106. Yang, T., et al. (2017). "Surface-engineered quantum dots/electrospun nanofibers as a networked fluorescence aptasensing platform toward biomarkers." *Nanoscale* 9(43): 17020-17028.
  107. Yang, Y., et al. (2017). "Hyaluronic Acid Conjugated Magnetic Prussian Blue@Quantum Dot Nanoparticles for Cancer Theranostics." *Theranostics* 7(2): 466-481.
  108. Yao, C., et al. (2017). "Tumor Cell-Specific Nuclear Targeting of Functionalized Graphene Quantum Dots In Vivo." *Bioconjug Chem* 28(10): 2608-2619.
  109. Zalgeviciene, V., et al. (2017). "Quantum dots mediated embryotoxicity via placental damage." *Reprod Toxicol* 73: 222-231.
  110. 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.
  111. Zhang, D., et al. (2018). "Mitochondrial specific photodynamic therapy by rare-earth nanoparticles mediated near-infrared graphene quantum dots." *Biomaterials* 153: 14-26.

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