Quantum and Cancer Biology Research Literatures

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

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1. Introduction

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

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

Abdul Manaf, S. A., G. Hedge, et al. "Functionalized Carbon Nano-scale drug delivery systems From Biowaste Sago Bark For Cancer Cell Imaging." Curr Drug Deliv. 2016 Oct 17.

BACKGROUND: Nano-scale carbon systems are emerging alternatives in drug delivery and bioimaging applications of which they gradually replace the quantum dots characterized by toxic heavy metal content in the latter application. OBJECTIVE: The work intended to use carbon nanospheres synthesized from biowaste Sago bark for cancer cell imaging applications. METHODS: This study synthesised carbon nanospheres from biowaste Sago bark using a catalyst-free pyrolysis technique. The nanospheres were functionalized with fluorescent dye coumarin-6 for cell imaging. Fluorescent nanosytems were characterized by field emission scanning electron microscopy-energy dispersive X ray, photon correlation spectroscopy and fourier transform infrared spectroscopy techniques. RESULTS: The average size of carbon nanospheres ranged between 30 and 40 nm with zeta potential of -26.8 +/- 1.87 mV. The percentage viability of cancer cells on exposure to nanospheres varied from 91-89 % for N2a cells and 90-85 % for A-375 cells respectively. Speedy uptake of the fluorescent nanospheres in both N2a and A-375 cells was observed within two hours of exposure. CONCLUSION: Novel fluorescent carbon nanosystem design following waste-to-wealth approach exhibited promising potential in cancer cell imaging applications.

Abeyasinghe, N., S. Kumar, et al. "Enhanced Emission from Single Isolated Gold Quantum Dots Investigated Using Two-Photon-Excited Fluorescence Near-Field Scanning Optical Microscopy." J Am Chem Soc. 2016 Dec 21;138(50):16299-16307. doi: 10.1021/jacs.6b07737. Epub 2016 Dec 13.

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 Au25 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.

Abeydeera, N. D., M. Egli, et al. "Evoking picomolar binding in RNA by a single phosphorodithioate linkage." Nucleic Acids Res. 2016 Sep 30;44(17):8052-64. doi: 10.1093/nar/gkw725. Epub 2016 Aug 26.

RNA aptamers are synthetic oligonucleotide-based affinity molecules that utilize unique three-dimensional structures for their affinity and specificity to a target such as a protein. They hold the promise of numerous advantages over biologically produced antibodies; however, the binding affinity and specificity of RNA aptamers are often insufficient for successful implementation in diagnostic assays or as therapeutic agents. Strong binding affinity is important to improve the downstream applications. We report here the use of the phosphorodithioate (PS2) substitution on a single nucleotide of RNA aptamers to dramatically improve target binding affinity by approximately 1000-fold (from nanomolar to picomolar). An X-ray co-crystal structure of the alpha-thrombin:PS2-aptamer complex reveals a localized induced-fit rearrangement of the PS2-containing nucleotide which leads to enhanced target interaction. High-level quantum mechanical calculations for model systems that mimic the PS2 moiety and phenylalanine demonstrate that an edge-on interaction between sulfur and the aromatic ring is quite favorable, and also confirm that the sulfur analogs are much more polarizable than the corresponding phosphates. This favorable interaction involving the sulfur atom is likely even more significant in the full aptamer-protein complexes than in the model systems.

Agarwal, S., G. Tyagi, et al. "Structural-conformational aspects of tRNA complexation with chloroethyl nitrosourea derivatives: A molecular modeling and spectroscopic investigation." J Photochem Photobiol B. 2017 Jan;166:1-11. doi: 10.1016/j.jphotobiol.2016.09.045. Epub 2016 Nov 6.

Chloroethyl nitrosourea derivatives (CENUs) represent an important family of anticancer chemotherapeutic agents, which are used in the treatment of different types of cancer such as brain tumors, resistant or relapsed Hodgkin's disease, small cell lung cancer and malignant melanoma. This work focuses towards understanding the interaction of chloroethyl nitrosourea derivatives; lomustine, nimustine and semustine with tRNA using spectroscopic approach in order to elucidate their auxiliary anticancer action mechanism inside the cell. Attenuated total reflection-Fourier transform infrared spectroscopy (ATR-FTIR), Fourier transform infrared difference spectroscopy, circular dichroism spectroscopy and UV-visible spectroscopy were employed to investigate the binding parameters of tRNA-CENUs complexation. Results of present study demonstrate that all CENUs, studied here, interact with tRNA through guanine nitrogenous base residues and possibly further crosslink cytosine residues in paired region of tRNA. Moreover, spectral data collected for nimustine-tRNA and semustine-tRNA complex formation indicates towards the groove-directed-alkylation as their anti-malignant action, which involves the participation of uracil moiety located in major groove of tRNA. Besides this, tRNA-CENUs adduct formation did not alter the native conformation of biopolymer and tRNA remains in A-form after its interaction with all three nitrosourea derivatives studied. The binding constants (Ka) estimated for tRNA complexation with lomustine, nimustine and semustine are 2.55x102M-1, 4.923x102M-1 and 4.223x102M-1 respectively, which specify weak type of CENU's binding with tRNA. Moreover, molecular modeling simulations were also performed to predict preferential binding orientation of CENUs with tRNA that corroborates well with spectral outcomes. The findings, presented here, recognize tRNA binding properties of CENUs that can further help in rational designing of more specific and efficient RNA targeted chemotherapeutic agents.

Agarwalla, H., P. S. Mahajan, et al. "A Switch-On NIR Probe for Specific Detection of Hg2+ Ion in Aqueous Medium and in Mitochondria." Inorg Chem. 2016 Nov 21;55(22):12052-12060. Epub 2016 Nov 10.

A new 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPY)-based probe molecule (L) is synthesized for specific binding to Hg2+ ion in physiological condition with an associated luminescence ON response in the near-IR region of the

spectrum. Appropriate functionalization in the 5-position of each of two pyrrole moieties with styryl functionality in a BODIPY core helped us in achieving the extended conjugation and a facile intramolecular charge transfer transition with a narrow energy gap for frontier orbitals. This accounted for a poor emission quantum yield for the probe molecule L. Binding to Hg2+ helped in interrupting the facile intramolecular charge transfer (ICT) process that was initially operational for L. This resulted in a hypsochromic shift of absorption band and a turn-on luminescence response with lambdaMaxEms of 650 nm on specific binding to Hg2+. Observed spectral changes are rationalized based on quantum chemical calculations. Interestingly, this reagent is found to be localized preferentially in the mitochondria of the live human colon cancer (Hct116) cells. Mitochondria is one of the major targets for localization of Hg2+, which actually decreases the mitochondrial membrane potential and modifies various proteins having sulfudryl functionality(ies) to cause cell apoptosis. Considering these, ability of the present reagent to specifically recognize Hg2+ in the mitochondrial region of the live Hct116 cells has significance.

Akhter, M. H. and S. Amin "An Investigative Approach to Treatment Modalities for Squamous Cell Carcinoma of Skin." Curr Drug Deliv. 2016 Sep 6.

Squamous cell carcinoma of skin has become an important matter of discussion worldwide due to high number of deaths. Treatment of such cancer involves use of drugs (chemotherapy) along with surgery or radiation therapy. The combination therapy is always preferred than single treatment modality due to poor internalization of most of the chemotherapeutics in the affected cells. Now a days, nanoparticle based drug delivery to squamous cell carcinoma is equanimous to become a leading therapeutic approach for cancer treatment. As nanoparticles are potentially delivered to the targeted cells with higher selectivity, minimal toxicity, better retention in the cell and long duration of retention, an effective therapeutic approach is seen. Passive chemotherapeutic approach is one of the leading therapies to such cancer cells due specific selectivity towards the EGFR-receptors over-expressed in tumor cells. But, due to innate toxicity of chemotherapeutic agents, active tumor targeting is considered desirable for therapeutic regime. Numerous approaches and strategies have been designed till date for successful delivery of drug to cancer cells. In this review, we have highlighted different therapeutic approaches such as nanoparticles (NPs), solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), gold NPs, silica NPs, nanocapsules, nanospheres, liposomes, dendrimers, nanocell, nanotube, fullerenes and quantum dots for active tumor targeting. Approaches such as receptor based drug targeting through molecular signal transduction pathways involved in skin cancer development and other such challenges in drug delivery to squamous cell carcinoma are also discussed to provide insight into squamous carcinoma.

Albert, K. and H. Y. Hsu "Carbon-Based Materials for Photo-Triggered Theranostic Applications." Molecules. 2016 Nov 20;21(11). pii: E1585.

Carbon-based nanomaterials serve as a type of smart material for photo-triggered disease theranostics. The inherent physicochemical properties of these nanomaterials facilitate their use for less invasive treatments. This review summarizes the properties and applications of materials including fullerene, nanotubes, nanohorns, nanodots and nanographenes for photodynamic nanomedicine in cancer and antimicrobial therapies. Carbon nanomaterials themselves do not usually act as photodynamic therapy (PDT) agents owing to the high hydrophobicity, however, when the surface is passivated or functionalized, these materials become great vehicles for PDT. Moreover, conjugation of carbonaceous nanomaterials with the photosensitizer (PS) and relevant targeting ligands enhances properties such as selectivity, stability, and high quantum yield, making them readily available for versatile biomedical applications.

Alemayehu, A. B., N. U. Day, et al. "Gold Tris(carboxyphenyl)corroles as Multifunctional Materials: Room Temperature Near-IR Phosphorescence and Applications to Photodynamic Therapy and Dye-Sensitized Solar Cells." ACS Appl Mater Interfaces. 2016 Jul 27;8(29):18935-42. doi: 10.1021/acsami.6b04269. Epub 2016 Jul 14.

Two amphiphilic corroles-5,10,15-tris(3-carboxyphenyl)corrole (H3[mTCPC]) and 5,10,15-tris(4-carboxyphenyl)corrole (H3[pTCPC])-and their gold complexes have been synthesized, and their photophysical properties and photovoltaic behavior have been investigated. Like other nonpolar gold corroles, Au[mTCPC] and Au[pTCPC] were both found to exhibit room temperature phosphorescence in deoxygenated solutions with quantum yields of approximately 0.3% and triplet lifetimes of approximately 75 mus. Both compounds exhibited significant activity as dyes in photodynamic therapy experiments and in dye-sensitized solar cells. Upon irradiation at 435 nm, both Au corroles exhibited significant phototoxicity against AY27 rat bladder cancer cells while the free-base corroles proved inactive. Dye-sensitized solar cells constructed using the free bases H3[mTCPC] and H3[pTCPC] exhibited low efficiencies (<<1%), well under that obtained with

5,10,15,20-tetrakis(4-carboxyphenyl)porphyrin, H2[pTCPP] (1.9%, cf. N719 9.5%). Likewise, Au[pTCPC] proved inefficient, with an efficiency of approximately 0.2%. By contrast, Au[mTCPC] proved remarkably effective, exhibiting an open-circuit voltage (Voc) of 0.56 V, a short-circuit current of 8.7 mA cm(-2), a fill factor of 0.72, and an efficiency of 3.5%.

Ang, H., M. Bosman, et al. "Highly Luminescent Heterostructured Copper-Doped Zinc Sulfide Nanocrystals for Application in Cancer Cell Labeling." Chemphyschem. 2016 Aug 18;17(16):2489-95. doi: 10.1002/cphc.201600415. Epub 2016 Jun 7.

The structural characteristics of the seed-mediated synthesis of heterostructured CuS-ZnS nanocrystals (NCs) and Cu-doped ZnS (ZnS:Cu) NCs synthesized by two different protocols are compared and analyzed. At high Cu dopant concentrations, segregated subclusters of ZnS and CuS are observed. The photoluminescence quantum yield of ZnS:Cu NCs is about 50-80 %; a value much higher than that of ZnS NCs (6 %). Finally, these NCs are coated with a thin silica shell by using (3-mercaptopropyl)triethoxysilane in a reverse microemulsion to make them water soluble. Cytotoxicity experiments show that these silica-coated NCs have greatly reduced toxicity on both cancerous HeLa and noncancerous Chinese hamster ovary cells. The labeling of cancerous HeLa cells is also demonstrated.

Atanasova, S., B. Nikolova, et al. "Electroinduced Delivery of Hydrogel Nanoparticles in Colon 26 Cells, Visualized by Confocal Fluorescence System." Anticancer Res. 2016 Sep;36(9):4601-6.

Nano-scale drug delivery systems (nano-DDS) are under intense investigation. Nano-platforms are developed for specific administration of small molecules, drugs, genes, contrast agents [quantum dots (QDs)] both in vivo and in vitro. Electroporation is a biophysical phenomenon which consists of the application of external electrical pulses across the cell membrane. The aim of this study was to research electro-assisted Colon 26 cell line internalization of QDs and QD-loaded nano-hydrogels (polymersomes) visualized by confocal microscopy and their influence on cell viability. The experiments were performed on the Colon 26 cancer cell line, using a confocal fluorescent imaging system and cell viability test. Electroporation facilitated the delivery of nanoparticles in vivo. We demonstrated increased voltage-dependent delivery of nanoparticles into cells after electrotreatment, without significant cell viability reduction. The delivery and retention of the polymersomes in vitro is a promising tool for future cancer treatment strategies and nanomedcine.

Bacchus-Montabonel, M. C. and F. Calvo "Influence of microhydration on the structures and proton-induced charge transfer in RNA intermediates." J Mol Model. 2016 Nov;22(11):262. Epub 2016 Oct 11.

Solvation effects are of major interest in the context of radiation damage, due to their potential applications in cancer therapy. Reliable modeling of the solvent is, however, quite challenging, and numerous studies have been devoted to isolated biomolecules and stepwise-hydrated molecules in which the amount of solvent is controlled one molecule at a time. The influence of stepwise hydration on radiation damage is investigated here using the example of proton-induced charge transfer in two biomolecular targets. Uracil has been widely investigated both experimentally and theoretically in this context, and 2-aminooxazole was recently shown to be a potentially important intermediate in prebiotic chemistry. Focusing here on doubly hydrated biomolecules, stable structures and infrared spectra were obtained by combining the results of molecular dynamics simulations with those of quantum chemistry calculations performed at the density-functional theory level with the double hybrid M06-2X functional. The charge-transfer cross-sections upon proton impact were obtained from ab initio molecular calculations and after applying a semi-classical approach to investigate the collision. Our results suggest a significant relationship between the detailed hydration structure and the efficacy of proton-induced charge transfer, highlighting the competing roles of inter- and intramolecular hydrogen bonding.

Bajwa, N., N. Kumar Mehra, et al. "Targeted anticancer drug delivery through anthracycline antibiotic bearing functionalized quantum dots." Artif Cells Nanomed Biotechnol. 2016 Nov;44(7):1774-82. doi: 10.3109/21691401.2015.1102740. Epub 2015 Oct 27.

We herein first report a method for the synthesis of chitosan (CHI)-folate conjugated colloidal ZnO-Mn(+2) quantum dots (QDs) bearing doxorubicin through chemical method (DOX/FA-CHI-QDs) for cancer therapy as well imaging purpose. The entrapment efficiency was determined to be 99.98 +/- 0.012% (DOX/FA-CHI-QDs) and 92.0 +/- 2.62% (DOX-QDs). The developed DOX/FA-CHI-QDs formulations depict the sustained release pattern at the lysosomal pH (pH 5.0). The DOX/FA-CHI-QDs showed enhanced cytotoxicity, cellular uptake and were most preferentially taken up by the cancerous cells via receptor-mediated endocytosis (RME) mechanism. Hence, the QD-based formulation is capable of targeting drug delivery and imaging the

delivery process.

Bauer, M. R., R. N. Jones, et al. "Harnessing Fluorine-Sulfur Contacts and Multipolar Interactions for the Design of p53 Mutant Y220C Rescue Drugs." ACS Chem Biol. 2016 Aug 19;11(8):2265-74. doi: 10.1021/acschembio.6b00315. Epub 2016 Jun 21.

Many oncogenic mutants of the tumor suppressor p53 are conformationally unstable, including the frequently occurring Y220C mutant. We have previously developed several small-molecule stabilizers of this mutant. One of these molecules, PhiKan083, 1-(9-ethyl-9H-carbazole-3-yl)-N-methylmethanamine, binds to a mutation-induced surface crevice with a KD = 150 muM, thereby increasing the melting temperature of the protein and slowing its rate of aggregation. Incorporation of fluorine atoms into small molecule ligands can substantially improve binding affinity to their protein targets. We have, therefore, harnessed fluorine-protein interactions to improve the affinity of this ligand. Step-wise introduction of fluorines at the carbazole ethyl anchor, which is deeply buried within the binding site in the Y220C-PhiKan083 complex, led to a 5-fold increase in affinity for a 2,2,2-trifluoroethyl anchor (ligand efficiency of 0.3 kcal mol(-1) atom(-1)). High-resolution crystal structures of the Y220C-ligand complexes combined with quantum chemical calculations revealed favorable interactions of the fluorines with protein backbone carbonyl groups (Leu145 and Trp146) and the sulfur of Cys220 at the mutation site. Affinity gains were, however, only achieved upon trifluorination, despite favorable interactions of the mono- and difluorinated anchors with the binding pocket, indicating a trade-off between energetically favorable protein-fluorine interactions and increased desolvation penalties. Taken together, the optimized carbazole scaffold provides a promising starting point for the development of high-affinity ligands to reactivate the tumor suppressor function of the p53 mutant Y220C in cancer cells.

Bensasson, R. V., A. T. Dinkova-Kostova, et al. "Electron affinity of tricyclic, bicyclic, and monocyclic compounds containing cyanoenones correlates with their potency as inducers of a cytoprotective enzyme." Bioorg Med Chem Lett. 2016 Sep 1;26(17):4345-9. doi: 10.1016/j.bmcl.2016.07.028. Epub 2016 Jul 15.

Tricyclic, bicyclic, and monocyclic compounds containing cyanoenones induce various anti-inflammatory and cytoprotective enzymes through activation of the Keap1/Nrf2/ARE (antioxidant response element) pathway. The potency of these compounds as Nrf2 activators was determined using a prototypic cytoprotective enzyme NAD(P)H: quinone oxidoreductase 1 (NQO1) in Hepa1c1c7 murine hepatoma cells. The electron affinity (EA) of the compounds, expressed as the energy of their lowest unoccupied molecular orbital [E (LUMO)], was evaluated using two types of quantum mechanical calculations: the semiempirical (AM1) and the density functional theory (DFT) methods. We observed striking linear correlations [r=0.897 (AM1) and 0.936 (DFT)] between NQO1 inducer potency of these compounds and their E (LUMO) regardless of the molecule size. Importantly and interestingly, this finding demonstrates that the EA is the essentially important factor that determines the reactivity of the cyanoenones with Keap1.

Blake, S. J., Z. Cheng, et al. "In silico investigation of factors affecting the MV imaging performance of a novel water-equivalent EPID." Phys Med. 2016 Dec;32(12):1819-1826. doi: 10.1016/j.ejmp.2016.09.019. Epub 2016 Oct 13.

PURPOSE: A Geant4 model of a novel, water-equivalent electronic portal imaging device (EPID) prototype for radiotherapy imaging and dosimetry utilising an array of plastic scintillating fibres (PSFs) has been developed. Monte Carlo (MC) simulations were performed to quantify the PSF-EPID imaging performance and to investigate design aspects affecting performance for optimisation. METHODS: Using the Geant4 model, the PSF-EPID's imaging performance for 6 MV photon beams was quantified in terms of its modulation transfer function (MTF), noise power spectrum (NPS) and detective quantum efficiency (DQE). Model parameters, including fibre dimensions, optical cladding reflectivity and scintillation yield, were varied to investigate impact on imaging performance. RESULTS: The MC-calculated DQE(0) for the reference PSF-EPID geometry employing 30mm fibres was approximately nine times greater than values reported for commercial EPIDs. When using 10mm long fibres, the PSF-EPID DQE(0) was still approximately three times greater than that of a commercial EPID. Increased fibre length, cladding reflectivity and scintillation yield produced the greatest decreases in NPS and increases in DQE. CONCLUSIONS: The potential to develop an optimised next-generation water-equivalent EPID with MV imaging performance at least comparable to commercial EPIDs has been demonstrated. Factors most important for optimising prototype design include fibre length, cladding reflectivity and scintillation yield.

Bujnakova, Z., M. Balaz, et al. "Mechanochemical approach for the capping of mixed core CdS/ZnS nanocrystals: Elimination of cadmium toxicity." J Colloid Interface Sci. 2017 Jan 15;486:97-111. doi:

10.1016/j.jcis.2016.09.033. Epub 2016 Sep 15.

The wet mechanochemical procedure for the capping of the CdS and CdS/ZnS quantum dot nanocrystals is reported. l-cysteine and polyvinylpyrrolidone (PVP) were used as capping agents. When using l-cysteine, the dissolution of cadmium(II) was almost none for CdS/ZnS nanocrystals. Moreover, prepared CdS- and CdS/ZnS-cysteine nanosuspensions exhibited unimodal particle size distributions with very good stability, which was further supported by the zeta potential measurements. The Fourier-transform infrared (FTIR) and nuclear magnetic resonance (NMR) spectroscopy showed the successful embedment of cysteine into the structure of the nanocrystals. Additionally, the optical properties were examined, and the results showed that the cysteine nanosuspension has promising fluorescence properties. On the other hand, PVP was not determined to be a very suitable capping agent for the present system. In this case, the release of cadmium(II) was higher in comparison to the l-cysteine capped samples. The nanosuspensions were successfully used for in vitro studies on selected cancer cell lines. Using fluorescence microscopy, it was evidenced that the nanocrystals enter the cell and that they can serve as imaging agents in biomedical applications.

Caceres, J., J. Robinson-Duggon, et al. "Photochemical behavior of biosupramolecular assemblies of photosensitizers, cucurbit[n]urils and albumins." Phys Chem Chem Phys. 2017 Jan 6. doi: 10.1039/c6cp07749h.

Biosupramolecular assemblies combining cucurbit[n]urils (CB[n]s) and proteins for the targeted delivery of drugs have the potential to improve the photoactivity of photosensitizers used in the photodynamic therapy of cancer. Understanding the complexity of these systems and how it affects the properties of photosensitizers is the focus of this work. We used acridine orange (AO+) as a model photosensitizer and compared it with methylene blue (MB+) and a cationic porphyrin (TMPyP4+). Encapsulation of the photosensitizers into CB[n]s (n = 7, 8) modified their photoactivity. In particular, for AO+, the photo-oxidation of HSA was enhanced in the presence of CB[7]; meanwhile it was decreased when included into CB[8]. Accordingly, peroxide generation and protein fragmentation were also increased when AO+ was encapsulated into CB[7]. The triplet excited state lifetimes of all the photosensitizers were lengthened by their encapsulation into CB[n]s, while the singlet oxygen quantum yield was enhanced only for AO+ and TMPyP4+, but it decreased for MB+. The results obtained in this work prompt the necessity of further investigating these kinds of hybrid assemblies as drug delivery systems because of their possible applications in biomedicine.

Cai, X., Y. Luo, et al. "pH-Sensitive ZnO Quantum Dots-Doxorubicin Nanoparticles for Lung Cancer Targeted Drug Delivery." ACS Appl Mater Interfaces. 2016 Aug 31;8(34):22442-50. doi: 10.1021/acsami.6b04933. Epub 2016 Aug 19.

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

Cao, Y., H. Dong, et al. "Aptamer-Conjugated Graphene Quantum Dots/Porphyrin Derivative Theranostic Agent for Intracellular Cancer-Related MicroRNA Detection and Fluorescence-Guided Photothermal/Photodynamic Synergetic Therapy." ACS Appl Mater Interfaces. 2017 Jan 11;9(1):159-166. doi: 10.1021/acsami.6b13150. Epub 2016 Dec 22.

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

generation up to 1.08, which enabled it to accomplish advanced photothermal therapy (PTT) and efficient photodynamic therapy (PDT) for cancer treatment. The combined PTT/PDT synergic therapy led to an outstanding therapeutic efficiency for cancer cell treatment.

Chan, M. H., C. W. Chen, et al. "Near-Infrared Light-Mediated Photodynamic Therapy Nanoplatform by the Electrostatic Assembly of Upconversion Nanoparticles with Graphitic Carbon Nitride Quantum Dots." Inorg Chem. 2016 Oct 17;55(20):10267-10277. Epub 2016 Sep 26.

Photodynamic therapy (PDT) is a promising antitumor treatment that is based on photosensitizers. This therapy kills cancer cells by generating reactive oxygen species (ROS) after irradiation with specific laser wavelengths. Being a potential photosensitizer, graphitic carbon nitride (g-C3N4) quantum dots (QDs) are noncytotoxic. Although the use of g-C3N4 QDs is challenged by the limited tissue penetration of UV light, g-C3N4 QDs display excellent ultraviolet (UV) light-triggered cytotoxicity. The g-C3N4 QDs were synthesized using a solid-phase hydrothermal method. The well-distributed hydrophilic g-C3N4 can be combined with NaYF4:Yb3+/Tm3+ upconversion nanoparticles via the positive ligand poly(l-lysine) to produce the final nanocomposite, NaYF4:Yb/Tm-PLL@g-C3N4. Upconversion nanoparticles can transfer IR light into UV light and promote g-C3N4 to release blue-to-green visible light to generate different images. Moreover, g-C3N4 is a promising photosensitizer in PDT because g-C3N4 can transfer oxygen into toxic ROS. The singlet oxygen formed by g-C3N4 displays great potential for use in the treatment of cancer.

Chen, H., T. Wang, et al. "Effects of surface modification of quantum dots on viability and migration of triple-negative breast cancer cells." J Colloid Interface Sci. 2017 Jan 1;485:51-58. doi: 10.1016/j.jcis.2016.09.024. Epub 2016 Sep 13.

Triple-negative breast cancer (BC) shows strong metastasis and has a bad prognosis. There are few effective approaches until date to detect BC cells at an early stage. Quantum dots (QDs) are one of the most promising nanomaterials for the detection of BC cells. QDs are usually modified with some functional molecules, such as PEG and BSA, to decrease or possibly eliminate their toxicity. Although a large number of studies have investigated the cytotoxicity of QDs, the effects of surface modification of QDs on biological behaviors of triple-negative BC cells remain unclear. In this work, QDs were prepared using the hydrothermal method and chemically modified with PEG and BSA. The optical performance of QDs was recorded with a digital camera. Their absorption and fluorescence (FL) properties were analyzed by UV-Vis spectrometer and FL spectrophotometer, respectively. The effects of QDs and surface modification on viability and migration were principally investigated. The possible mechanism was primarily analyzed. The results show that QDs exhibit excellent optical performance under ultraviolet irradiation. Surface modification slightly reduces the photon count reaching the QDs surface. Moreover, surface modification results in a blue-shift of FL peak of QDs, which is ascribed to the change in surface chemical environment because of PEG and BSA modifications. In addition, QDs, PEG coated QDs (PEG@CdTe) and BSA coated QDs (BSA@CdTe) can reduce viability and inhibit migration of BC cells. The inhibition effects are time- and concentration-dependent. In addition, PEG and BSA modified QDs exhibit lower inhibition effects on BC cells, as compared with unmodified QDs. In this process, Reactive oxygen species (ROS) does not appear to play an important role, and other pathways should be considered. This work provides experimental support and useful clinical guidance for QDs-applications in BC detection.

Chen, Z., R. Liang, et al. "Simultaneous quantitation of cytokeratin-19 fragment and carcinoembryonic antigen in human serum via quantum dot-doped nanoparticles." Biosens Bioelectron. 2016 Dec 13;91:60-65. doi: 10.1016/j.bios.2016.12.036.

A novel quantum dot-doped polystyrene nanoparticles-based lateral flow test strips (QPs-LFTS) system was developed to simultaneously detect a cytokeratin-19 fragment (CYFRA 21-1) and carcinoembryonic antigen (CEA) in human serum to aid the diagnosis and prognosis of lung cancer. Quantum dot-doped carboxylate-functionalized polystyrene nanoparticles (QPs) were prepared and introduced as fluorescent reporters in QPs-LFTS. The detection was based on a sandwich immunoassay and performed on lateral flow test strips, with an assay time of 15min. The strips were read by a fluorescence strip reader to obtain the fluorescence peak heights of the test lines (HT) and the control line (HC). The ratio of HT/HC was used for quantitation. The QPs showed excellent photoproperties and good performance. Under optimal conditions, the QPs-LFTS system exhibited a wide linear range for CYFRA 21-1 (1.3-480ng/mL) and CEA (2.8-680ng/mL). The detection limits for CYFRA 21-1 and CEA were 0.16 and 0.35ng/mL, respectively. The recovery and reproducibility of the method were satisfactory. Furthermore, excellent correlations (n =120, R2 =0.9862, P<0.0001 for CYFRA 21-1; n =70, R2 =0.9509, P<0.0001 for CEA) were obtained between the QPs-LFTS and commercially available

chemiluminescence immunoassay kits in clinical serum testing. The results indicate that this developed test system is highly efficient and is expected to be useful for early screening and prognosis evaluation for lung cancer patients.

Cheng, J., W. Li, et al. "Synthesis and in vitro photodynamic therapy of chlorin derivative 131-ortho-trifluoromethyl-phenylhydrazone modified pyropheophorbide-a." Biomed Pharmacother. 2017 Jan 4;87:263-273. doi: 10.1016/j.biopha.2016.12.081.

Photodynamic therapy (PDT) is entering the mainstream of the cancer treatments recently. Pyropheophorbide-a (Pa), as a degradation product of chlorophyll-a, has been shown to be a potent photosensitizer in photodynamic therapy. In this paper, we investigated the in vitro photodynamic therapy of 131-ortho-trifluoromethyl-phenylhydrazone modified pyropheophorbide-a (PHPa) against human HeLa cervical cancer cell line, together with ultraviolet-visible spectra, fluorescence emission spectra, stability in various solvents, and single oxygen quantum yield. The results indicated that PHPa not only showed a greater molar extinction coefficient reached 4.55x104 Lmol-1cm-1, the long absorption wavelength (681nm) as we expected that makes it potential in deep tumor treatment, but also showed better stability in near neutral phosphate buffers (pH 7.4) and culture medium, as well as higher single oxygen quantum yield (capital EF, CyrillicD=40.5%) in DMF solutions. Moreover, cell experiments suggested that PHPa could be uptaken by HeLa cells successfully, and has low dark toxicity without irradiation, but remarkable photo-cytotoxicity (IC50, 1.92+/-0.59muM) that the inhibition rate of HeLa cells could increase up 91.4% at 30muM of PHPa after irradiation. In addition, morphological changes of HeLa cells further demonstrated that PHPa can induce damage and apoptotic cell death. Furthermore, the mechanism of photochemical processes was investigated by using specific quenching agent sodium azide (SA) and D-mannitol (DM), respectively, which showed the formation of singlet oxygen (Type II reaction mechanism) may play a predominant role, Type I and Type II photodynamic reactions could occur simultaneously in this PHPa mediated PDT process.

Chiou, J. W., B. Fu, et al. "Blocking the Interactions between Calcium-Bound S100A12 Protein and the V Domain of RAGE Using Tranilast." PLoS One. 2016 Sep 6;11(9):e0162000. doi: 10.1371/journal.pone.0162000. eCollection 2016.

The receptor for advanced glycation end products (RAGE), a transmembrane receptor in the immunoglobulin superfamily, is involved in several inflammatory processes. RAGE induces cellular signaling pathways upon binding with various ligands, such as advanced glycation end products (AGEs), beta-amyloids, and S100 proteins. The solution structure of S100A12 and the V ligand-binding region of RAGE have been reported previously. Using heteronuclear NMR spectroscopy to conduct 1H-15N heteronuclear single quantum coherence (HSQC) titration experiments, we identified and mapped the binding interface between S100A12 and the V domain of RAGE. The NMR chemical shift data were used as the constraints for the High Ambiguity Driven biomolecular DOCKing (HADDOCK) calculation to generate a structural model of the S100A12-V domain complex. In addition, tranilast (an anti-allergic drug) showed strong interaction with S100A12 in the 1H-15N HSQC titration, fluorescence experiments, and WST-1 assay. The results also indicated that tranilast was located at the binding site between S100A12 and the V domain, blocking interaction between these two proteins. Our results provide the mechanistic details for a structural model and reveal a potential precursor for an inhibitor for pro-inflammatory diseases, which could be useful for the development of new drugs.

Chiu, S. H., G. Gedda, et al. "Rapid fabrication of carbon quantum dots as multifunctional nanovehicles for dual-modal targeted imaging and chemotherapy." Acta Biomater. 2016 Dec;46:151-164. doi: 10.1016/j.actbio.2016.09.027. Epub 2016 Sep 20.

Herein, we synthesized an S, N, and Gd tri-element doped magnetofluorescent carbon quantum dots (GdNS@CQDs) within 10min by using a one-pot microwave method. Our results showed that these magnetofluorescent GdNS@CQDs have excellent fluorescent and magnetic properties. Moreover, GdNS@CQDs exhibited high stability at physiological conditions and ionic strength. These magnetofluorescent GdNS@CQDs were conjugated with a folic acid, denoted as FA-GdNS@CQDs, for targeting dual modal fluorescence/magnetic resonance (MR) imaging. The in vitro and in vivo studies confirmed the high biocompatibility and low toxicity of FA-GdNS@CQDs. FA-GdNS@CQDs enhanced the MR response as compared to that for commercial Gd-DTPA. The targeting capabilities of FA-GdNS@CQDs were confirmed in HeLa and HepG2 cells using in vitro fluorescence and MR dual modality imaging. Additionally, an anticancer drug, doxorubicin, was incorporated into the FA-GdNS@CQDs forming FA-GdNS@CQDs-DOX, which enables targeted drug delivery. Importantly, the prepared FA-GdNS@CQDs-DOX showed a high quantity of doxorubicin loading capacity (about 80%) and pH-sensitive drug release. The uptake into cancer cells and the intracellular location of the FA-GdNS@CQDs were observed by confocal laser scanning microscopy. We also

successfully demonstrated in vivo fluorescence bio imaging of the FA-GdNS@CQDs, using zebrafish as an animal model. STATEMENT OF SIGNIFICANCE: In this manuscript, we reported a facial, rapid, and environmental friendly method to fabricate hetero atoms including gadolinium, nitrogen, and sulfur doped multi-functional magnetofluorescent carbon quantum dots (GdNS@CQDs) nanocomposite. These multifunctional GdNS@CQDs were conjugated with a folic acid for targeting dual modal fluorescence/magnetic resonance imaging. Additionally, an anticancer drug, doxorubicin, was incorporated into the nanocomposite forming FA-GdNS@CQDs-DOX, which enables targeted drug delivery. We have developed GdNS@CQDs with integrated functions for simultaneous in vitro cell imaging, targeting, and pH-sensitive controlled drug release in HeLa cells. Furthermore, we successfully demonstrated the use of this material for in vivo fluorescence imaging, using zebrafish as an animal model.

Cho, C. C., R. H. Chou, et al. "Amlexanox Blocks the Interaction between S100A4 and Epidermal Growth Factor and Inhibits Cell Proliferation." PLoS One. 2016 Aug 25;11(8):e0161663. doi: 10.1371/journal.pone.0161663. eCollection 2016.

The human S100A4 protein binds calcium, resulting in a change in its conformation to promote the interaction with its target protein. Human epidermal growth factor (EGF) is the target protein of S100A4 and a critical ligand of the receptor EGFR. The EGF/EGFR system promotes cell survival, differentiation, and growth by activating several signaling pathways. Amlexanox is an anti-inflammatory and anti-allergic drug that is used to treat recurrent aphthous ulcers. In the present study, we determined that amlexanox interacts with S100A4 using heteronuclear single quantum correlation titration. We elucidated the interactions of S100A4 with EGF and amlexanox using fluorescence and nuclear magnetic resonance spectroscopy. We generated two binary models (for the S100A4-EGF and S100A4-amlexanox complexes) and observed that amlexanox and EGF share a similar binding region in mS100A4. We also used a WST-1 assay to investigate the bioactivity of S100A4, EGF, and amlexanox, and found that amlexanox blocks the binding between S100A4 and EGF, and is therefore useful for the development of new anti-proliferation drugs.

Choi, S. Y., S. H. Baek, et al. "Synthesis of upconversion nanoparticles conjugated with graphene oxide quantum dots and their use against cancer cell imaging and photodynamic therapy." Biosens Bioelectron. 2016 Aug 28. pii: S0956-5663(16)30851-X. doi: 10.1016/j.bios.2016.08.094.

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

Choudhary, R., S. Patra, et al. "Designing of carbon based fluorescent nanosea-urchin via green-synthesis approach for live cell detection of zinc oxide nanoparticle." Biosens Bioelectron. 2016 Dec 31;91:472-481. doi: 10.1016/j.bios.2016.12.067.

The present work reports an eco-friendly and economic method for the preparation of different shaped (spherical, rod, and sea-urchin) heteroatom-doped fluorescent carbon nanoparticles (CNPs) by a unique combination of sonochemical, microwave and hydrothermal approach. Not only in terms of chemical, herein, we used the green precursors i.e. six members from solonaceae family for the synthesis of CNPs. Among the various shapes of CNPs, the sea-urchin shape CNPs (SU-CNPs) shows the high product and quantum yield with good photostability, excellent water dispersibility, narrow size distribution and high storage ability. The high quantum yield of derived CNPs made them suitable for patterning and staining (fluorescent inks) as a better, economic and eco-friendly replacement of dyes. In addition, the synthesized SU-CNPs were employed for quantitative detection of a widely used nanomaterial i.e. zinc oxide nanoparticles (ZnO). The fluorescence sensor was successfully applied for the detection of ZnO nanoparticles in wastewater, human sera and some cosmetic samples without any cross-reactivity. Herein,

for the first time, we have successfully used the SU-CNPs for live cell detection of ZnO nanoparticles. The in vitro cytocompatibility study demonstrated that the SU-CNPs were not harmful to the cell up to a very high concentration of 1500.0mgL-1 and could be used for cell imaging. In addition, the SU-CNPs were successfully utilized for the qualitative and quantitative, intracellular detection of ZnO nanoparticle in breast cancer cell line i.e. MCF-7.

Chua, E. G., M. J. Wise, et al. "Quantum changes in Helicobacter pylori gene expression accompany host-adaptation." DNA Res. 2016 Nov 1. pii: dsw046.

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

Chung, H., P. R. Poulsen, et al. "Reconstruction of implanted marker trajectories from cone-beam CT projection images using interdimensional correlation modeling." Med Phys. 2016 Aug;43(8):4643. doi: 10.1118/1.4958678.

PURPOSE: Cone-beam CT (CBCT) is a widely used imaging modality for image-guided radiotherapy. Most vendors provide CBCT systems that are mounted on a linac gantry. Thus, CBCT can be used to estimate the actual 3-dimensional (3D) position of moving respiratory targets in the thoracic/abdominal region using 2D projection images. The authors have developed a method for estimating the 3D trajectory of respiratory-induced target motion from CBCT projection images using interdimensional correlation modeling. METHODS: Because the superior-inferior (SI) motion of a target can be easily analyzed on projection images of a gantry-mounted CBCT system, the authors investigated the interdimensional correlation of the SI motion with left-right and anterior-posterior (AP) movements while the gantry is rotating. A simple linear model and a state-augmented model were implemented and applied to the interdimensional correlation analysis, and their performance was compared. The parameters of the interdimensional correlation models were determined by least-square estimation of the 2D error between the actual and estimated projected target position. The method was validated using 160 3D tumor trajectories from 46 thoracic/abdominal cancer patients obtained during CyberKnife treatment. The authors' simulations assumed two application scenarios: (1) retrospective estimation for the purpose of moving tumor setup used just after volumetric matching with CBCT; and (2) on-the-fly estimation for the purpose of real-time target position estimation during gating or tracking delivery, either for full-rotation volumetric-modulated arc therapy (VMAT) in 60 s or a stationary six-field intensity-modulated radiation therapy (IMRT) with a beam delivery time of 20 s. RESULTS: For the retrospective CBCT simulations, the mean 3D root-mean-square error (RMSE) for all 4893 trajectory segments was 0.41 mm (simple linear model) and 0.35 mm (state-augmented model). In the on-the-fly simulations, prior projections over more than 60 degrees appear to be necessary for reliable estimations. The mean 3D RMSE during beam delivery after the simple linear model had established with a prior 90 degrees projection data was 0.42 mm for VMAT and 0.45 mm for IMRT. CONCLUSIONS: The proposed method does not require any internal/external correlation or statistical modeling to estimate the target trajectory and can be used for both retrospective image-guided radiotherapy with CBCT projection images and real-time target position monitoring for respiratory gating or tracking.

Cortopassi, W. A., K. Kumar, et al. "Cation-pi interactions in CREBBP bromodomain inhibition: an electrostatic model for small-molecule binding affinity and selectivity." Org Biomol Chem. 2016 Nov 22;14(46):10926-10938.

CREBBP bromodomains, epigenetic "reader" proteins that recognize acetylated histone lysine residues, are a current target for cancer therapy. We show that experimental CREBBP binding affinities of small-molecules with aromatic or heteroaromatic functional groups are strongly influenced by a cation-pi interaction with a positively charged arginine residue. For a series of fifteen 5-isoxazolylbenzimidazole derivatives, the strength of

this non-covalent interaction is directly related to improvements in binding to CREBBP. The aromatic substituents' inductive and resonance effects are not obviously correlated with observed structure and affinity relationships. In contrast, a coulombic electrostatic model can quantitatively predict the interaction strength. We have assessed different Molecular Mechanics (MM) and Quantum Mechanics (QM) descriptions of the protein-ligand interaction. Quantitative models for binding affinity were generated from: (1) Poisson Boltzmann Surface Area (MM-PBSA) and Generalized Born Surface Area (MM-GBSA) scoring functions that incorporated the entire ligand and (2) QM-complexation energies and (3) Electrostatic Potential Surface values (ESPs) that analyzed the varying aromatic group. A linear relationship between QM-computed ESP values is established for the cation-pi interaction strength, and gives the best correlation (R2 = 0.84) with experimental binding affinities. This model also ranks ligand affinity most accurately (rs = 0.91) from the models tested. Consideration of the electrostatic potential in response to the local effects of substituents in addition to that of the aromatic ring is necessary to understand and describe the interaction with the cationic guanidinium ion. This leads to an improved understanding and the ability to quantitatively predict the magnitude of non-covalent interactions in the CREBBP active site.

Deepagan, V. G., D. G. You, et al. "Long-Circulating Au-TiO2 Nanocomposite as a Sonosensitizer for ROS-Mediated Eradication of Cancer." Nano Lett. 2016 Oct 3.

Although sonodynamic therapy (SDT) has emerged as a potential alternative to conventional photodynamic therapy, the low quantum yield of the sonosensitizer such as TiO2 nanoparticles (NPs) is still a major concern. Here, we have developed hydrophilized Au-TiO2 nanocomposites (HAu-TiO2 NCs) as sonosensitizers for improved SDT. The physicochemical properties of HAu-TiO2 NCs were thoroughly studied and compared with their counterparts without gold deposition. Upon exposure of HAu-TiO2 NCs to ultrasound, a large quantity of reactive oxygen species (ROS) were generated, leading to complete suppression of tumor growth after their systemic administration in vivo. Overall, it was evident that the composites of gold with TiO2 NPs significantly augmented the levels of ROS generation, implying their potential as SDT agents for cancer therapy.

Deglmann, C. J., K. Blazkow-Schmalzbauer, et al. "Cadmium Telluride Quantum Dots as a Fluorescence Marker for Adipose Tissue Grafts." Ann Plast Surg. 2017 Feb;78(2):217-222. doi: 10.1097/SAP.0000000000000930.

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, mercaptoproprionic acid-coated cadmium telluride quantum dots (QDs) emitting in the dark red or near infrared. The intracellular localization of QDs was studied by confocal laser scanning microscopy.As a result, the adipose tissue clusters showed a proportional increase in fluorescence with increasing concentrations (1, 10, 16, 30, 50 nM) of cadmium telluride QDs. Laser scanning microscopy demonstrated a membrane bound localization of QDs. Vacuoles and cell nuclei of adipocytes were spared by QDs. We conclude that QDs were for the first time proven intracellular in adult adipocytes and demonstrate a strong fluorescence signal. Therefore, they may play an essential role for in vivo tracking of fat grafts.

Deng, H., Q. Liu, et al. "Quantum dots-labeled strip biosensor for rapid and sensitive detection of microRNA based on target-recycled nonenzymatic amplification strategy." Biosens Bioelectron. 2017 Jan 15;87:931-940. doi: 10.1016/j.bios.2016.09.043. Epub 2016 Sep 12.

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

(qRT-PCR). Clinical tumor samples were also tested, and 16 of 20 samples gave out positive signals, which demonstrated the practical application capacity of the biosensor. Therefore, the proposed biosensor holds great promise for potential POC applications and early cancer diagnosis.

Ding, C., L. Tong, et al. "Recent Advances in Stimuli-Responsive Release Function Drug Delivery Systems for Tumor Treatment." Molecules. 2016 Dec 20;21(12). pii: E1715. doi: 10.3390/molecules21121715.

Benefiting from the development of nanotechnology, drug delivery systems (DDSs) with stimuli-responsive controlled release function show great potential in clinical anti-tumor applications. By using a DDS, the harsh side effects of traditional anti-cancer drug treatments and damage to normal tissues and organs can be avoided to the greatest extent. An ideal DDS must firstly meet bio-safety standards and secondarily the efficiency-related demands of a large drug payload and controlled release function. This review highlights recent research progress on DDSs with stimuli-responsive characteristics. The first section briefly reviews the nanoscale scaffolds of DDSs, including mesoporous nanoparticles, polymers, metal-organic frameworks (MOFs), quantum dots (QDs) and carbon nanotubes (CNTs). The second section presents the main types of stimuli-responsive mechanisms and classifies these into two categories: intrinsic (pH, redox state, biomolecules) and extrinsic (temperature, light irradiation, magnetic field and ultrasound) ones. Clinical applications of DDS, future challenges and perspectives are also mentioned.

Duan, S., Y. Yang, et al. "NIR-Responsive Polycationic Gatekeeper-Cloaked Hetero-Nanoparticles for Multimodal Imaging-Guided Triple-Combination Therapy of Cancer." Small. 2016 Dec 20. doi: 10.1002/smll.201603133.

Responsive multifunctional organic/inorganic nanohybrids are promising for effective and precise imaging-guided therapy of cancer. In this work, a near-infrared (NIR)-triggered multifunctional nanoplatform comprising Au nanorods (Au NRs), mesoporous silica, quantum dots (QDs), and two-armed ethanolamine-modified poly(glycidyl methacrylate) with cyclodextrin cores (denoted as CD-PGEA) has been successfully fabricated for multimodal imaging-guided triple-combination treatment of cancer. A hierarchical hetero-structure is first constructed via integration of Au NRs with QDs through a mesoporous silica intermediate layer. The X-ray opacity and photoacoustic (PA) property of Au NRs are utilized for tomography (CT) and PA imaging, and the imaging sensitivity is further enhanced by the fluorescent QDs. The mesoporous feature of silica allows the loading of a typical antitumor drug, doxorubicin (DOX), which are sealed by the polycationic gatekeepers, low toxic hydroxyl-rich CD-PGEA/pDNA complexes, realizing the co-delivery of drug and gene. The photothermal effect of Au NRs is utilized for photothermal therapy (PTT). More interestingly, such photothermal effect also induces a cascade of NIR-triggered release of DOX through the facilitated detachment of CD-PGEA gatekeepers for controlled chemotherapy. The resultant chemotherapy and gene therapy for glioma tumors are complementary for the efficiency of PTT. This work presents a novel responsive multifunctional imaging-guided therapy platform, which combines fluorescent/PA/CT imaging and gene/chemo/photothermal therapy into one nanostructure.

Duong, T., X. Li, et al. "Phototheranostic nanoplatform based on a single cyanine dye for image-guided combinatorial phototherapy." Nanomedicine. 2016 Nov 21. pii: S1549-9634(16)30197-6. doi: 10.1016/j.nano.2016.11.005.

This study represents a novel phototheranostic nanoplatform based on the near-infrared (NIR) heptamethine cyanine dye, IR775, which is capable of concurrent real-time fluorescence imaging and cancer eradication with combinatorial phototherapy. To achieve water solubility and enhance tumor delivery, the hydrophobic IR775 dye was loaded into a biocompatible polymeric nanoparticle with a diameter of ~40nm and slightly negative surface charge (-2.34mV). The nanoparticle-encapsulated hydrophobic IR775 dye (IR775-NP) is characterized by an enhanced fluorescence quantum yield (16%) when compared to the water soluble analogs such as ICG (2.7%) and IR783 (8%). Furthermore, the developed IR-775-NP efficiently generates both heat and reactive oxygen species under NIR light irradiation, eradicating cancer cells in vitro. Finally, animal studies revealed that the IR775-NP accumulates in cancer tumors after systemic administration, efficiently delineates them with NIR fluorescence signal and completely eradicates chemo resistant cancer tissue after a single dose of combinatorial phototherapy.

Elzoghby, A. O., A. L. Hemasa, et al. "Hybrid protein-inorganic nanoparticles: From tumor-targeted drug delivery to cancer imaging." J Control Release. 2016 Dec 10;243:303-322. doi: 10.1016/j.jconrel.2016.10.023. Epub 2016 Oct 26.

Recently, a great interest has been paid to the development of hybrid protein-inorganic nanoparticles (NPs) for drug delivery and cancer diagnostics in order to combine the merits of both inorganic and protein nanocarriers. This review primarily discusses the most

outstanding advances in the applications of the hybrids of naturally-occurring proteins with iron oxide, gadolinium, gold, silica, calcium phosphate NPs, carbon nanotubes, and quantum dots in drug delivery and cancer imaging. Various strategies that have been utilized for the preparation of protein-functionalized inorganic NPs and the mechanisms involved in the drug loading process are discussed. How can the protein functionalization overcome the limitations of colloidal stability, poor dispersibility and toxicity associated with inorganic NPs is also investigated. Moreover, issues relating to the influence of protein hybridization on the cellular uptake, tumor targeting efficiency, systemic circulation, mucosal penetration and skin permeation of inorganic NPs are highlighted. A special emphasis is devoted to the novel approaches utilizing the protein-inorganic nanohybrids in combined cancer therapy, tumor imaging, and theranostic applications as well as stimuli-responsive drug release from the nanohybrids.

Enjeti, A. K., A. Ariyarajah, et al. "Correlative analysis of nanoparticle tracking, flow cytometric and functional measurements for circulating microvesicles in normal subjects." Thromb Res. 2016 Sep;145:18-23. doi: 10.1016/j.thromres.2016.06.029. Epub 2016 Jun 29.

INTRODUCTION: Circulating microvesicles (MV) can be analysed using a number of different techniques. The aim of this study was to evaluate the correlation between functional procoagulant based assays including thrombin generation, factor Xa activation test (XaCT), and phosphatidylserine factor Xa-activity by ELISA with optical MV enumeration by flow cytometry and nanoparticle tracking analysis. METHODS: Citrated blood samples were collected from 60 healthy volunteer blood donors after informed consent. Platelet free plasma was prepared using a standardized published protocol. MV subsets were enumerated by flow cytometry (BDFACS Canto) after staining with specific antibodies for platelets (CD41), endothelial cells (CD105), red cells (CD235) monocytes (CD14), tissue factor (CD142) and for phosphatidylserine expression by binding to annexin V. A standardized protocol using counting beads was employed. Nanotracking analysis was performed on both scatter and fluorescent settings after MV staining with quantum dot stain, Qdot 655. Procoagulant function was assessed by the XaCT assay on an automated coagulation analyser and by thrombin generation assay measuring endogenous thrombin potential (ETP), lagtime, peak (PEAK) and time to peak (ttPEAK) using a Calibrated Automated Thrombogram (CAT). The statistical analysis was carried out with Statistica 12 software using non-parametric tests (Spearman rank order correlations, with significance set at $p<0.05$). RESULTS: In normal healthy subjects, thrombin generation parameters correlated with levels of MV measured by flow cytometry. ETP, lagtime, ttPEAK and PEAK correlated with MV expressing phosphatidylserine (rs, Spearman rank order correlation was 0.29, 0.40, 0.31 and 0.34 respectively, $p<0.05$), and MV expressing tissue factor (rs was 0.29, 0.40, 0.31 and 0.34 respectively, $p<0.05$), whilst red cell derived MV correlated with lagtime, ttPEAK and PEAK (rs, was 0.35,0.30 and 0.3, respectively, $p<0.05$). Lagtime and ttPEAK negatively correlated with the clot based XaCT test (rs, was -0.34 and -0.30 respectively, $p<0.05$) and positively correlated with the ELISA MP-activity assay ($rs=0.42$ for both, $p<0.05$). In addition, endothelial MV levels weakly correlated with white cell counts ($rs = 0.27$, $p<0.05$). CONCLUSIONS: Thrombin generation and flow cytometry for phosphatidylserine or tissue factor expressing MV correlate well as markers for procoagulant activity. A combination of optical or non-optical enumeration as well as functional methods may be required for a complete profiling of circulating MV.

Erasmus, M. F., K. Matlawska-Wasowska, et al. "Dynamic pre-BCR homodimers fine-tune autonomous survival signals in B cell precursor acute lymphoblastic leukemia." Sci Signal. 2016 Nov 29;9(456):ra116.

The pre-B cell receptor (pre-BCR) is an immature form of the BCR critical for early B lymphocyte development. It is composed of the membrane-bound immunoglobulin (Ig) heavy chain, surrogate light chain components, and the signaling subunits Igalpha and Igbeta. We developed monovalent quantum dot (QD)-labeled probes specific for Igbeta to study the behavior of pre-BCRs engaged in autonomous, ligand-independent signaling in live B cells. Single-particle tracking revealed that QD-labeled pre-BCRs engaged in transient, but frequent, homotypic interactions. Receptor motion was correlated at short separation distances, consistent with the formation of dimers and higher-order oligomers. Repeated encounters between diffusing pre-BCRs appeared to reflect transient co-confinement in plasma membrane domains. In human B cell precursor acute lymphoblastic leukemia (BCP-ALL) cells, we showed that frequent, short-lived, homotypic pre-BCR interactions stimulated survival signals, including expression of BCL6, which encodes a transcriptional repressor. These survival signals were blocked by inhibitory monovalent antigen-binding antibody fragments (Fabs) specific for the surrogate light chain components of the pre-BCR or by inhibitors of the tyrosine kinases Lyn and Syk. For comparison, we evaluated pre-BCR aggregation mediated by dimeric

galectin-1, which has binding sites for carbohydrate and for the surrogate light chain lambda5 component. Galectin-1 binding resulted in the formation of large, highly immobile pre-BCR aggregates, which was partially relieved by the addition of lactose to prevent the cross-linking of galectin-BCR complexes to other glycosylated membrane components. Analysis of the pre-BCR and its signaling partners suggested that they could be potential targets for combination therapy in BCP-ALL.

Feng, G., Y. Fang, et al. "Multifunctional Conjugated Polymer Nanoparticles for Image-Guided Photodynamic and Photothermal Therapy." Small. 2017 Jan;13(3). doi: 10.1002/smll.201602807. Epub 2016 Nov 7.

A multifunctional theranostic platform based on conjugated polymer nanoparticles (CPNs) with tumor targeting, fluorescence detection, photodynamic therapy (PDT), and photothermal therapy (PTT) is developed for effective cancer imaging and therapy. Two conjugated polymers, poly[9,9-bis(2-(2-(2-methoxyethoxy)ethoxy)-ethyl)fluorenyldivinylene]-alt-4,7-(2, 1,3-benzothiadiazole) with bright red emission and photosensitizing ability and poly[(4,4,9,9-tetrakis(4-(octyloxy)phenyl)-4,9-dihydro-s-indacenol-dithiophene-2, 7-diyl)-alt-co-4,9-bis(thiophen-2-yl)-6,7-bis(4-(hexyloxy)phenyl)-thiadiazolo-qui noxaline] with strong near-infrared absorption and excellent photothermal conversion ability are co-loaded into one single CPN via encapsulation approach using lipid-polyethylene glycol as the matrix. The obtained co-loaded CPNs show sizes of around 30 nm with a high singlet oxygen quantum yield of 60.4% and an effective photothermal conversion efficiency of 47.6%. The CPN surface is further decorated with anti-HER2 affibody, which bestows the resultant anti-HER2-CPNs superior selectivity toward tumor cells with HER2 overexpression both in vitro and in vivo. Under light irradiation, the PDT and PTT show synergistic therapeutic efficacy, which provides new opportunities for the development of multifunctional biocompatible organic materials in cancer therapy.

Feng, G., W. Wu, et al. "Far Red/Near-Infrared AIE Dots for Image-Guided Photodynamic Cancer Cell Ablation." ACS Appl Mater Interfaces. 2016 Aug 24;8(33):21193-200. doi: 10.1021/acsami.6b06136. Epub 2016 Aug 10.

We report a facile encapsulation approach to realize bright far red/near-infrared (FR/NIR) fluorescence and efficient singlet oxygen ((1)O2) production of organic fluorogens with aggregation-induced emission (AIEgen) and intramolecular charge transfer (ICT) characteristics for image-guided photodynamic cancer cell ablation. The synthesized AIEgen BTPEAQ possesses donor-acceptor-donor structure, which shows bright fluorescence in solid state. Due to the strong ICT effect, BTPEAQ exhibits poor emission with almost no (1)O2 generation in aqueous solution. Encapsulation of BTPEAQ by DSPE-PEG block copolymer yields polymer-shelled dots, which show enhanced brightness with a fluorescence quantum yield of 3.9% and a (1)O2 quantum yield of 38%. Upon encapsulation by silica, the formed SiO2-shelled dots show much improved fluorescence quantum yield of 12.1% but with no obvious (1)O2 generation. This study clearly demonstrates the importance of encapsulation approach for organic fluorophores, which affects not only the brightness but also the (1)O2 production. After conjugating the polymer-shelled AIE dots with cRGD peptide, the obtained BTPEAQ-cRGD dots show excellent photoablation toward MDA-MB-231 cells with integrin overexpression while keeping control cells intact.

Feng, Q. M., Z. Zhou, et al. "DNA tetrahedral scaffolds-based platform for the construction of electrochemiluminescence biosensor." Biosens Bioelectron. 2017 Apr 15;90:251-257. doi: 10.1016/j.bios.2016.11.060. Epub 2016 Nov 27.

Proximal metallic nanoparticles (NPs) could quench the electrochemiluminescence (ECL) emission of semiconductor quantum dots (QDs) due to Forster energy transfer (FRET), but at a certain distance, the coupling of light-emission with surface plasmon resonance (SPR) result in enhanced ECL. Thus, the modification strategies and distances control between QDs and metallic NPs are critical for the ECL intensity of QDs. In this strategy, a SPR enhanced ECL sensor based on DNA tetrahedral scaffolds modified platform was reported for the detection of telomerase activity. Due to the rigid three-dimensional structure, DNA tetrahedral scaffolds grafting on the electrode surface could accurately modulate the distance between CdS QDs and luminol labelled gold nanoparticles (L-Au NPs), meanwhile provide an enhanced spatial dimension and accessibility for the assembly of multiple L-Au NPs. The ECL intensities of both CdS QDs (-1.25V vs. SCE) and luminol (+0.33V vs. SCE) gradually increased along with the formation of multiple L-Au NPs at the vertex of DNA tetrahedral scaffolds induced by telomerase, bringing in a dual-potential ECL analysis. The proposed method showed high sensitivity for the identification of telomerase and was successfully applied for the differentiation of cancer cells from normal cells. This work suggests that DNA tetrahedral scaffolds could serve as an excellent choice for the construction of SPR-ECL system.

Feng, Y., L. Liu, et al. "Four-photon-excited fluorescence resonance energy transfer in an aqueous system from ZnSe:Mn/ZnS quantum dots to hypocrellin A." Opt Express. 2016 Aug 22;24(17):19627-37. doi: 10.1364/OE.24.019627.

In this work, we established a fluorescence resonance energy transfer (FRET) system between ZnSe:Mn/ZnS quantum dots and Hypocrellin A (HA, a photosensitizer used for photodynamic therapy of cancer) in aqueous solution, excited by four-photon. Here, the QDs are the donors and the HA are the acceptors. The four-photon-excited fluorescence resonance energy transfer spectrum was obtained under 1300nm femtosecond laser pluses. The experimental results indicated that the highest efficiency of FRET can reach up to 61.3%. Furthermore, the viability test in cancer cells was further demonstrated for biological applications of FRET system. When FRET occurs the cell killing rate of the cancer cells will reach to 84.8% with the 1mM concentration of HA. Our work demonstrates that while the four-photon excited FRET system is promising in both optics and biological applications, is also needs further investigation.

Ferreira, D. P., D. S. Conceicao, et al. "Porphyrin dye into biopolymeric chitosan films for localized photodynamic therapy of cancer." Carbohydr Polym. 2016 Oct 20;151:160-71. doi: 10.1016/j.carbpol.2016.05.060. Epub 2016 May 19.

Porphyrins and some of its derivatives are well known and widely used as photosensitizers (PSs) for Photodynamic Therapy of Cancer (PDT). The present study regards the characterization and evaluation of a synthesized asymmetric porphyrin dye in solution to be used as PS for PDT. This molecule was also incorporated into biopolymeric films composed by chitosan, polyethylene glycol (PEG) and gelatin in order to overtake some of the disadvantages inherent to the PS, but more important, to evaluate the potential of a system composed by the porphyrin/biopolymer to be applied as localized therapeutic agents. FTIR spectroscopy showed a strong interaction between the polymers involved in the preparation of the films under study: film 1: chitosan, film 2: chitosan/PEG and film 3: chitosan/gelatin. Photochemical studies were performed for the dye in solution and into the three different biopolymeric films. Ground state absorption showed the characteristic bands of these kinds of dyes in solution and also incorporated into the films. The films composed by porphyrin/chitosan and porphyrin into chitosan/gelatin, revealed the presence of non-emissive aggregates exhibiting a strong quenching effect in the fluorescence intensity, quantum yields and lifetimes. In this way, the system composed by the porphyrin incorporated into the chitosan/PEG film presents the best fluorescence quantum yield and lifetime. The transient absorption spectra were obtained for all the systems indicating the formation of an excited triplet state of the porphyrins following excitation, which takes special importance in the generation of phototoxic species namely singlet oxygen. Singlet oxygen quantum yields were also determined and the results obtained were very promising for the dye in solution but also for the dye into the different substrates. The release of the dye from the three different films onto a buffer solution was evaluated and we conclude that after a few days the dye was completely released by the substrates in acidic conditions. Confocal microscopy was used for the determination of the intracellular localization of the compound under study onto HeLa cells (human cervical cancer cells line). The evaluation of the PSs anticancer activity assumes special importance for PDT studies. The system should be less toxic in the dark and more active when irradiated, therefore, toxicity in the dark and phototoxicity studies onto HeLa cells were performed.

Fukunaga, H., A. Yokoya, et al. "Now Is the Time to Consider Personalized Effective Dose." Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2):479-80. doi: 10.1016/j.ijrobp.2016.06.012. Epub 2016 Jun 20.

Gao, C., L. Zhang, et al. "Visible-light driven biofuel cell based on hierarchically branched titanium dioxide nanorods photoanode for tumor marker detection." Biosens Bioelectron. 2016 Sep 15;83:327-33. doi: 10.1016/j.bios.2016.04.049. Epub 2016 Apr 19.

In this work, a novel sensing platform based on visible light driven biofuel cell (BFC) has been facilely designed for sensitive detection of prostate-specific antigen (PSA) with the photo-response bioanode, realizing the dual route energy conversion of light energy and chemical energy to electricity. The hierarchical branched TiO2 nanorods (B-TiO2 NRs) decorated with CdS quantum dots (QDs) act as the substrate to confine glucose dehydrogenase (GDH) for the visible light driven glucose oxidation at the bioanode. Three dimensional flowers like hierarchical carbon/gold nanoparticles/bilirubin oxidase (3D FCM/AuNPs/BOD) bioconjugate served as biocatalyst for O2 reduction at the biocathode. With an increase in the concentration of PSA, the amount of BOD labels on biocathode increases, thus leading to the higher current output of the as-proposed visible light driven BFC. Based on this, this sensing platform provide great performance in sensitivity and specificity, increasing linear detection range from 0.3pgmL(-1) to 7mugmL(-1) with a detection limit of 0.1pgmL(-1).

Most importantly, our new sensing strategy provided a simple and inexpensive sensing platform for tumor markers detection, suggesting its wide potential applications for clinical diagnostics.

Gao, J., C. Wu, et al. "Direct Synthesis of Water-Soluble Aptamer-Ag2 S Quantum Dots at Ambient Temperature for Specific Imaging and Photothermal Therapy of Cancer." Adv Healthc Mater. 2016 Sep;5(18):2437-49. doi: 10.1002/adhm.201600545. Epub 2016 Jul 8.

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

Gao, M., H. Su, et al. "Targeted imaging of EGFR overexpressed cancer cells by brightly fluorescent nanoparticles conjugated with cetuximab." Nanoscale. 2016 Aug 11;8(32):15027-32. doi: 10.1039/c6nr04439e.

To improve the treatment efficiency and reduce side effects in cancer therapy, accurate diagnosis of cancer cell types at a molecular level is highly desirable. Fluorescent nanoparticles (NPs) are especially suitable for detecting molecular biomarkers of cancer with advantages of superior brightness, easy decoration and high resolution. However, the conventional organic fluorophores, conjugated polymers, and inorganic quantum dots suffer from the drawbacks of aggregation-caused quenching (ACQ), low photostability, and heavy metal toxicity, respectively, which severely restrict their applications in NPs-based fluorescence imaging. To overcome these limitations, herein, we have developed fluorescent nanoparticles based on a t-BuPITBT-TPE fluorophore derived from aggregation-induced emission (AIE)-active tetraphenylethene. Through encapsulating t-BuPITBT-TPE within biocompatible DSPE-PEG and further decorating with a monoclonal antibody cetuximab (C225), the obtained t-BuPITBT-TPE-C225 NPs can be used for targeted imaging of non-small cell lung cancer cells with an overexpressed epidermal growth factor receptor (EGFR). The specific targeting ability of t-BuPITBT-TPE-C225 NPs has been well verified by confocal microscopy and flow cytometry experiments. The t-BuPITBT-TPE-C225 NPs have shown significant advantages in terms of highly efficient red emission, good bio-compatibility, and excellent photostability. This work provides a promising method for precise diagnosis of cancer cells by antibody-functionalized fluorescent NPs with high brightness.

Garcia-Cortes, M., J. R. Encinar, et al. "Highly sensitive nanoparticle-based immunoassays with elemental detection: Application to Prostate-Specific Antigen quantification." Biosens Bioelectron. 2016 Nov 15;85:128-34. doi: 10.1016/j.bios.2016.04.090. Epub 2016 Apr 27.

One of the major challenges in developing novel assay methods for the detection of biomolecules is achieving high sensitivity, because of the ultralow concentrations typically in clinical samples. Here, a Mn-doped ZnS quantum dots-based immunoassay platform is presented for highly sensitive detection of cancer biomarkers. Ultrahigh sensitivity is achieved through gold deposition on the surface of the nanoparticle tags acting as catalytic seeds, thus effectively amplifying the size of the metallic nanoparticles after the immunoassay and before the tag detection. Elemental mass spectrometry measurement of the gold content allowed detection of Prostate-Specific Antigen (PSA) at the low attog mL(-1) level. Moreover, the developed method showed not only an extremely high sensitivity for PSA detection but also a broad dynamic range, higher than 8 orders of magnitude, particularly useful for clinical studies involving quantitative detection of diverse biomarkers at their very different relevant concentration levels. Its applicability to discriminate small differences in PSA concentrations at low levels (few pgmL(-1)) in real serum samples was successfully evaluated.

Ge, S. M., D. L. Zhan, et al. "Reverse screening approach to identify potential anti-cancer targets of dipyridamole." Am J Transl Res. 2016 Dec 15;8(12):5187-5198. eCollection 2016.

Dipyridamole (DIP) inhibits thrombus formation when given chronically, and causes vasodilation over a short time. To date, DIP can increase the anticancer drugs (5-fluorouracil,

methotrexate, piperidine, vincristine) concentration in cancer cells and hence enhance the efficacy of treatment cancer. The inhibition of DIP may result in increased 5-fluorouracil efficacy and diminish the drug side effects. But the actual molecular targets remain unknown. In this study, reverse protein-ligands docking, and quantum mechanics were used to search for the potential molecular targets of DIP. The quantum mechanics calculation was performed by using Gaussian 03 program package. Reverse pharmacophore mapping was used to search for potential molecular target candidates for a given small molecule. The docking study was used for exploring the potential anti-cancer targets of dipyridamole. The two predicted binders with the statistically significant prediction are dihydropyrimidine dehydrogenase (DPD) (PDB Id: 1GTE) and human spindle checkpoint kinase Bub1 (PDB Id: 3E7E). Structure analysis suggests that electrostatic interaction and hydrogen bonding play an important role in their binding process. The strong functional linkage of DIP and 5FU supports our prediction. In conclusion, these results generate a tractable set of anticancer proteins. The exploration of polypharmacology will provide us new opportunities in treating systematic diseases, such as the cancers. The results would generate a tractable set of anticancer target proteins for future experimental validations.

Genc, M., Z. Karagoz Genc, et al. "Design, Synthesis, in vitro Antiproliferative Activity, Binding Modeling of 1,2,4,-Triazoles as New Anti-Breast Cancer Agents." Acta Chim Slov. 2016 Dec;63(4):726-737.

This article demonstrates the synthesis of 1,2,4-triazole derivatives and their applications in medicine particularly as anti-breast cancer agents which is a major issue of the present. The synthesized compounds were characterized by elemental analysis, FT-IR and NMR. DFT was used to study the quantum chemical calculations of geometries and vibrational wave numbers of 3-hydroxynaphthyl and p-tolyl substituted 1,2,4-triazoles in the ground state. The scaled harmonic vibrational frequencies obtained from the DFT method were compared with those of the FT-IR spectra and found good agreement. The synthesized 1,2,4-triazole-naphthyl hybrids were screened for the anticancer activity against MCF-7 breast cancer lines. Among them compounds 3 and 7 showed broad spectrum anticancer activity with IC50 values 9.7 muM and 7.10 muM, respectively and their activity is comparable to that of the standard drugs. The molecular model for binding between the compounds (1-8) and the active site of BRCA2 was obtained on the basis of the computational docking results and the structure-activity relationship.

Geng, X. F., M. Fang, et al. "Quantum dot-based molecular imaging of cancer cell growth using a clone formation assay." Mol Med Rep. 2016 Oct;14(4):3007-12. doi: 10.3892/mmr.2016.5632. Epub 2016 Aug 18.

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

Grinyte, R., J. Barroso, et al. "Microbead QD-ELISA: Microbead ELISA Using Biocatalytic Formation of Quantum Dots for Ultra High Sensitive Optical and Electrochemical Detection." ACS Appl Mater Interfaces. 2016 Nov 2;8(43):29252-29260. Epub 2016 Oct 24.

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 Cd2+ ions originating from immobilized CdS QDs showed linearity up to 45 ng mL-1, and the limit of SOD2 detection equal to 0.44 ng mL-1 (1.96 x 10-11 M). This detection limit is lower by 2 orders of magnitude in comparison with that of other previously published assays for superoxide dismutase. The electrochemical assay was validated with HepG2 (Human hepatocellular carcinoma) cell lysate containing SOD2.

Guerard, F., Y. S. Lee, et al. "Unexpected Behavior of the Heaviest Halogen Astatine in the Nucleophilic Substitution of Aryliodonium Salts." Chemistry. 2016 Aug 22;22(35):12332-9. doi: 10.1002/chem.201600922. Epub 2016 Jun 15.

Aryliodonium salts have become precursors of choice for the synthesis of (18) F-labeled tracers for nuclear imaging. However, little is known on the reactivity of these compounds with heavy halides, that is, radioiodide and astatide, at the radiotracer scale. In the first comparative study of radiohalogenation of aryliodonium salts with (125) I(-) and (211) At(-) , initial experiments on a model compound highlight the higher reactivity of astatide compared to iodide, which could not be anticipated from the trends previously observed within the halogen series. Kinetic studies indicate a significant difference in activation energy (Ea =23.5 and 17.1 kcal mol(-1) with (125) I(-) and (211) At(-) , respectively). Quantum chemical calculations suggest that astatination occurs via the monomeric form of an iodonium complex whereas iodination occurs via a heterodimeric iodonium intermediate. The good to excellent regioselectivity of halogenation and high yields achieved with diversely substituted aryliodonium salts indicate that this class of compounds is a promising alternative to the stannane chemistry currently used for heavy radiohalogen labeling of tracers in nuclear medicine.

Gulzar, A., P. Yang, et al. "Bioapplications of graphene constructed functional nanomaterials." Chem Biol Interact. 2017 Jan 25;262:69-89. doi: 10.1016/j.cbi.2016.11.019. Epub 2016 Nov 20.

Graphene has distinctive mechanical, electronic, and optical properties, which researchers have applied to develop innovative electronic materials including transparent conductors and ultrafast transistors. Lately, the understanding of various chemical properties of graphene has expedited its application in high-performance devices that generate and store energy. Graphene is now increasing its terrain outside electronic and chemical applications toward biomedical areas such as precise bio sensing through graphene-quenched fluorescence, graphene-enhanced cell differentiation and growth, and graphene-assisted laser desorption/ionization for mass spectrometry. In this Account, we evaluate recent efforts to apply graphene and graphene oxides (GO) to biomedical research and a few different approaches to prepare graphene materials designed for biomedical applications and a brief perspective on their future applications. Because of its outstanding aqueous processability, amphiphilicity, surface functionalizability, surface enhanced Raman scattering (SERS), and fluorescence quenching ability, GO chemically exfoliated from oxidized graphite is considered a promising material for biological applications. In addition, the hydrophobicity and flexibility of large-area graphene synthesized by chemical vapor deposition (CVD) allow this material to play an important role in cell growth and differentiation. Graphene is considered to be an encouraging and smart candidate for numerous biomedical applications such as NIR-responsive cancer therapy and fluorescence bio-imaging and drug delivery. To that end, suitable preparation and unique approaches to utilize graphene-based materials such as graphene oxides (GOs), reduced graphene oxides (rGOs), and graphene quantum dots (GQDs) in biology and medical science are gaining growing interest.

Gupta, B. K., S. Singh, et al. "Bifunctional Luminomagnetic Rare-Earth Nanorods for High-Contrast Bioimaging Nanoprobes." Sci Rep. 2016 Sep 2;6:32401. doi: 10.1038/srep32401.

Nanoparticles exhibiting both magnetic and luminescent properties are need of the hour for many biological applications. A single compound exhibiting this combination of properties is uncommon. Herein, we report a strategy to synthesize a bifunctional luminomagnetic Gd2-xEuxO3 (x = 0.05 to 0.5) nanorod, with a diameter of ~20 nm and length in ~0.6 mum, using hydrothermal method. Gd2O3:Eu(3+) nanorods have been characterized by studying its structural, optical and magnetic properties. The advantage offered by photoluminescent imaging with Gd2O3:Eu(3+) nanorods is that this ultrafine nanorod material exhibits hypersensitive intense red emission (610 nm) with good brightness (quantum yield more than 90%), which is an essential parameter for high-

contrast bioimaging, especially for overcoming auto fluorescent background. The utility of luminomagnetic nanorods for biological applications in high-contrast cell imaging capability and cell toxicity to image two human breast cancer cell lines T47D and MDA-MB-231 are also evaluated. Additionally, to understand the significance of shape of the nanostructure, the photoluminescence and paramagnetic characteristic of Gd2O3:Eu(3+) nanorods were compared with the spherical nanoparticles of Gd2O3:Eu(3+).

Han, H., D. Valdeperez, et al. "Dual Enzymatic Reaction-Assisted Gemcitabine Delivery Systems for Programmed Pancreatic Cancer Therapy." ACS Nano. 2017 Jan 10. doi: 10.1021/acsnano.6b05541.

Dual enzymatic reactions were introduced to fabricate programmed gemcitabine (GEM) nanovectors for targeted pancreatic cancer therapy. Dual-enzyme sensitive GEM nanovectors were prepared by conjugation of matrix metalloproteinase-9 (MMP-9) detachable poly(ethylene glycol) (PEG), cathepsin B cleavable GEM, and targeting ligand CycloRGD to CdSe/ZnS quantum dots (QDs). The GEM nanovectors decorated with PEG corona could avoid nonspecific interactions and exhibit prolonged blood circulation time. After GEM nanovectors were accumulated in tumor tissue by the enhanced permeability and retention (EPR) effect, the PEG corona can be removed by overexpressed MMP-9 in tumor tissue and RGD would be exposed, which was capable of facilitating cellular internalization. Once internalized into pancreatic cancer cells, the elevated lysosomal cathepsin B could further promote the release of GEM. By employing dual enzymatic reactions, the GEM nanovectors could achieve prolonged circulation time while maintaining enhanced cellular internalization and effective drug release. The proposed mechanism of the dual enzymatic reaction-assisted GEM delivery system was fully investigated both in vitro and in vivo. Meanwhile, compared to free GEM, the deamination of GEM nanovectors into inactive 2',2'-difluorodeoxyuridine (dFdU) could be greatly suppressed, while the concentration of the activated form of GEM (gemcitabine triphosphate, dFdCTP) was significantly increased in tumor tissue, thus exhibiting superior tumor inhibition activity with minimal side effects.

Hasanzadeh, M. and N. Shadjou "What are the reasons for low use of graphene quantum dots in immunosensing of cancer biomarkers?" Mater Sci Eng C Mater Biol Appl. 2017 Feb 1;71:1313-1326. doi: 10.1016/j.msec.2016.11.068. Epub 2016 Nov 26.

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

Heo, S., S. Yoo, et al. "Analysis of Neutron Production in Passively Scattered Ion-Beam Therapy." Radiat Prot Dosimetry. 2016 Nov 24.

A new treatment facility for heavy ion therapy since 2010 was constructed. In the broad beam, a range shifter, ridge filter and multi leaf collimator (MLC) for the generation of the spread-out Bragg peak is used. In this case, secondary neutrons produced by the interactions of the ion field with beam-modifying devices (e.g. double-scattering system, beam shaping collimators and range compensators) are very important for patient safety. Therefore, these components must be carefully examined in the context of secondary neutron yield and associated secondary cancer risk. In this article, Monte Carlo simulation has been carried out with the FLUktuierende KAskade particle transport code, the fluence and distribution of neutron generation and the neutron dose equivalent from the broad beam components are compared using carbon and proton beams. As a result, it is confirmed that the yield of neutron production using a carbon beam from all components of the broad beam was higher than using a proton beam. The ambient dose by neutrons per heavy ion and proton ion from the MLC surface was 0.12-0.18 and 0.0067-0.0087 pSv, respectively, which shows that heavy ions generate more neutrons than protons. However, ambient dose per treatment 2 Gy, which means physical dose during treatment by ion beam, is higher than carbon beam because proton therapy needs more beam flux to make 2-Gy prescription dose. Therefore, the neutron production from the MLC, which is closed to the patient, is a very important parameter for patient safety.

Hollstein, M., L. B. Alexandrov, et al. "Base changes in tumour DNA have the power to reveal the causes and evolution of cancer." Oncogene. 2017 Jan 12;36(2):158-167. doi: 10.1038/onc.2016.192. Epub 2016 Jun 6.

Next-generation sequencing (NGS)

technology has demonstrated that the cancer genomes are peppered with mutations. Although most somatic tumour mutations are unlikely to have any role in the cancer process per se, the spectra of DNA sequence changes in tumour mutation catalogues have the potential to identify the mutagens, and to reveal the mutagenic processes responsible for human cancer. Very recently, a novel approach for data mining of the vast compilations of tumour NGS data succeeded in separating and precisely defining at least 30 distinct patterns of sequence change hidden in mutation databases. At least half of these mutational signatures can be readily assigned to known human carcinogenic exposures or endogenous mechanisms of mutagenesis. A quantum leap in our knowledge of mutagenesis in human cancers has resulted, stimulating a flurry of research activity. We trace here the major findings leading first to the hypothesis that carcinogenic insults leave characteristic imprints on the DNA sequence of tumours, and culminating in empirical evidence from NGS data that well-defined carcinogen mutational signatures are indeed present in tumour genomic DNA from a variety of cancer types. The notion that tumour DNAs can divulge environmental sources of mutation is now a well-accepted fact. This approach to cancer aetiology has also incriminated various endogenous, enzyme-driven processes that increase the somatic mutation load in sporadic cancers. The tasks now confronting the field of molecular epidemiology are to assign mutagenic processes to orphan and newly discovered tumour mutation patterns, and to determine whether avoidable cancer risk factors influence signatures produced by endogenous enzymatic mechanisms. Innovative research with experimental models and exploitation of the geographical heterogeneity in cancer incidence can address these challenges.

Hu, Z., B. Song, et al. "Aqueous synthesized quantum dots interfere with the NF-kappaB pathway and confer anti-tumor, anti-viral and anti-inflammatory effects." Biomaterials. 2016 Nov;108:187-96. doi: 10.1016/j.biomaterials.2016.08.047. Epub 2016 Aug 31.

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

Huang, A., L. Zhou, et al. "Molecular design and validation of halogen bonding orthogonal to hydrogen bonding in breast cancer MDM2-peptide complex." J Mol Graph Model. 2016 Nov;70:40-44. doi: 10.1016/j.jmgm.2016.09.007. Epub 2016 Sep 13.

Peptide therapeutics has been raised as an attractive approach for the treatment of breast cancer by targeting the oncogenic protein MDM2 that inactivates p53 tumor suppressor. Here, we performed molecular design of halogen bonding orthogonal to hydrogen bonding at the complex interface of MDM2 protein with its cognate peptide ligand to improve the peptide binding affinity and specificity. Crystal structure analysis, high-level quantum chemistry (QC) calculations and combined quantum mechanics/molecular mechanics (QM/MM) modeling revealed that halogen substitution at position 3 of the benzene moiety of peptide Phe3 residue can constitute a putative halogen bonding, which is shown to be geometrically perpendicular to and energetically independent of a native hydrogen bonding that share a common carbonyl oxygen acceptor. The designed halogen bonding was then validated by surface plasmon resonance (SPR) assays, that is, substitution with bromine at position 3 can considerably improve peptide affinity by approximately 4-fold, but the peptide binding does not change substantially upon the bromine substitution at other positions of the Phe3 benzene moiety (the negative controls that are theoretically unable to form the halogen bonding), indicating that the orthogonal molecular interaction (OMI) system between the designed halogen bonding and native hydrogen bonding can co-work well at the complex interface of MDM2 protein with its halogenated peptide ligands.

Huang, L., Z. Li, et al. "Ultralow-Power Near Infrared Lamp Light Operable Targeted Organic Nanoparticle Photodynamic Therapy." J Am Chem Soc. 2016 Nov 9;138(44):14586-14591. Epub 2016 Oct 27.

Tissue penetration depth is a major challenge in practical photodynamic therapy (PDT). A biocompatible and highly effective near infrared (NIR)-light-absorbing carbazole-substituted BODIPY (Car-BDP) molecule is reported as a class of imaging-guidable deep-tissue activatable photosensitizers for PDT. Car-BDP possesses an intense, broad NIR absorption band (600-800 nm) with a remarkably high singlet oxygen quantum yield (PhiDelta = 67%). After being encapsulated with biodegradable PLA-PEG-FA polymers, Car-BDP can form uniform and small organic nanoparticles that are water-soluble and tumor-targetable. Rather than using laser light, such nanoparticles offer an unprecedented deep-tissue, tumor targeting photodynamic therapeutic effect by using an exceptionally low-power-density and cost-effective lamp light (12 mW cm-2). In addition, these nanoparticles can be simultaneously traced in vivo due to their excellent NIR fluorescence. This study signals a major step forward in photodynamic therapy by developing a new class of NIR-absorbing biocompatible organic nanoparticles for effective targeting and treatment of deep-tissue tumors. This work also provides a potential new platform for precise tumor-targeting theranostics and novel opportunities for future affordable clinical cancer treatment.

Hughes, T. B., N. L. Dang, et al. "Modeling Reactivity to Biological Macromolecules with a Deep Multitask Network." ACS Cent Sci. 2016 Aug 24;2(8):529-37. doi: 10.1021/acscentsci.6b00162. Epub 2016 Jul 29.

Most small-molecule drug candidates fail before entering the market, frequently because of unexpected toxicity. Often, toxicity is detected only late in drug development, because many types of toxicities, especially idiosyncratic adverse drug reactions (IADRs), are particularly hard to predict and detect. Moreover, drug-induced liver injury (DILI) is the most frequent reason drugs are withdrawn from the market and causes 50% of acute liver failure cases in the United States. A common mechanism often underlies many types of drug toxicities, including both DILI and IADRs. Drugs are bioactivated by drug-metabolizing enzymes into reactive metabolites, which then conjugate to sites in proteins or DNA to form adducts. DNA adducts are often mutagenic and may alter the reading and copying of genes and their regulatory elements, causing gene dysregulation and even triggering cancer. Similarly, protein adducts can disrupt their normal biological functions and induce harmful immune responses. Unfortunately, reactive metabolites are not reliably detected by experiments, and it is also expensive to test drug candidates for potential to form DNA or protein adducts during the early stages of drug development. In contrast, computational methods have the potential to quickly screen for covalent binding potential, thereby flagging problematic molecules and reducing the total number of necessary experiments. Here, we train a deep convolution neural network-the XenoSite reactivity model-using literature data to accurately predict both sites and probability of reactivity for molecules with glutathione, cyanide, protein, and DNA. On the site level, cross-validated predictions had area under the curve (AUC) performances of 89.8% for DNA and 94.4% for protein. Furthermore, the model separated molecules electrophilically reactive with DNA and protein from nonreactive molecules with cross-validated AUC performances of 78.7% and 79.8%, respectively. On both the site- and molecule-level, the model's performances significantly outperformed reactivity indices derived from quantum simulations that are reported in the literature. Moreover, we developed and applied a selectivity score to assess preferential reactions with the macromolecules as opposed to the common screening traps. For the entire data set of 2803 molecules, this approach yielded totals of 257 (9.2%) and 227 (8.1%) molecules predicted to be reactive only with DNA and protein, respectively, and hence those that would be missed by standard reactivity screening experiments. Site of reactivity data is an underutilized resource that can be used to not only predict if molecules are reactive, but also show where they might be modified to reduce toxicity while retaining efficacy. The XenoSite reactivity model is available at http://swami.wustl.edu/xenosite/p/reactivity.

Hwang, J. Y., S. T. Kim, et al. "Optical Aptamer Probes of Fluorescent Imaging to Rapid Monitoring of Circulating Tumor Cell." Sensors (Basel). 2016 Nov 23;16(11). pii: E1909.

Fluorescence detecting of exogenous EpCAM (epithelial cell adhesion molecule) or muc1 (mucin1) expression correlated to cancer metastasis using nanoparticles provides pivotal information on CTC (circulating tumor cell) occurrence in a noninvasive tool. In this study, we study a new skill to detect extracellular EpCAM/muc1 using quantum dot-based aptamer beacon (QD-EpCAM/muc1 ALB (aptamer linker beacon). The QD-EpCAM/muc1 ALB was designed using QDs (quantum dots) and probe. The EpCAM/muc1-targeting aptamer contains a Ep-CAM/muc1 binding sequence and BHQ1 (black hole quencher 1) or BHQ2 (black hole quencher2). In the absence of target EpCAM/muc1, the QD-

EpCAM/muc1 ALB forms a partial duplex loop-like aptamer beacon and remained in quenched state because the BHQ1/2 quenches the fluorescence signal-on of the QD-EpCAM/muc1 ALB. The binding of EpCAM/muc1 of CTC to the EpCAM/muc1 binding aptamer sequence of the EpCAM/muc1-targeting oligonucleotide triggered the dissociation of the BHQ1/2 quencher and subsequent signal-on of a green/red fluorescence signal. Furthermore, acute inflammation was stimulated by trigger such as caerulein in vivo, which resulted in increased fluorescent signal of the cy5.5-EpCAM/muc1 ALB during cancer metastasis due to exogenous expression of EpCAM/muc1 in Panc02-implanted mouse model.

Iannazzo, D., A. Pistone, et al. "Graphene quantum dots for cancer targeted drug delivery." Int J Pharm. 2017 Jan 2;518(1-2):185-192. doi: 10.1016/j.ijpharm.2016.12.060.

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.

Ivanova, D., Z. Zhelev, et al. "Overproduction of reactive oxygen species - obligatory or not for induction of apoptosis by anticancer drugs." Chin J Cancer Res. 2016 Aug;28(4):383-96. doi: 10.21147/j.issn.1000-9604.2016.04.01.

Many studies demonstrate that conventional anticancer drugs elevate intracellular level of reactive oxygen species (ROS) and alter redox-homeostasis of cancer cells. It is widely accepted that anticancer effect of these chemotherapeutics is due to induction of oxidative stress and ROS-mediated apoptosis in cancer. On the other hand, the harmful side effects of conventional anticancer chemotherapy are also due to increased production of ROS and disruption of redox-homeostasis of normal cells and tissues. This article describes the mechanisms for triggering and modulation of apoptosis through ROS-dependent and ROS-independent pathways. We try to answer the question: "Is it possible to induce highly specific apoptosis only in cancer cells, without overproduction of ROS, as well as without harmful effects on normal cells and tissues?" The review also suggests a new therapeutic strategy for selective killing of cancer cells, without significant impact on viability of normal cells and tissues, by combining anticancer drugs with redox-modulators, affecting specific signaling pathways and avoiding oxidative stress.

Jiang, S., Y. Yang, et al. "Co-evolution of tumor-associated macrophages and tumor neo-vessels during cervical cancer invasion." Oncol Lett. 2016 Oct;12(4):2625-2631. Epub 2016 Aug 16.

Considering the crucial significance of the tumor microenvironment in cancer development and progression, the present study aimed to investigate the changes in macrophages and angiogenesis during the cervical cancer (CC) progression process from chronic cervicitis to cervical intraepithelial neoplasia grades I-III (CIN I-III) to CC. This investigation included quantitative analysis and assessment of the spatial associations between tumor-associated macrophages (TAMs) and tumor neo-vessels. The conventional immunohistochemistry staining technique was used to detect cluster of differentiation (CD)68 and CD105 biomarker expression for TAMs and tumor neo-vessels, respectively. In addition, with the assistance of quantum dot (QD)-based two-component in situ imaging technology, the expression of the TAMs and tumor neo-vessels could be observed simultaneously. The quantitative analysis and co-evolution of the TAMs and tumor neo-vessels could then be processed. During the progression process from chronic cervicitis to cervical CIN I-III, and ultimately to invasive CC, the expression of the macrophages and neo-vessels in the tumor microenvironment increased synchronously. According to the quantitative analysis results, the median value of the TAM density was higher in the CC group (5,540.14) than in the CIN I-III group (2,502.17) and the chronic cervicitis group (1,403.31), with statistical significance in all three groups ($P<0.001$, for between-group comparisons). The number of neo-vessels was also much higher in the CC group (n=27) than in the CIN I-III group (n=17) or the chronic cervicitis group (n=6.5), with statistical significance in all three groups ($P<0.001$, for between-group comparisons). These findings demonstrated the great significance and close association of TAMs and tumor angiogenesis during CC development and progression. Thus, QDs-based in situ and simultaneous imaging of key cancer molecules may provide insights

with regard to the biology of cancer invasion.

Jing, L., S. V. Kershaw, et al. "Aqueous Based Semiconductor Nanocrystals." Chem Rev. 2016 Sep 28;116(18):10623-730. doi: 10.1021/acs.chemrev.6b00041. Epub 2016 Sep 2.

This review summarizes traditional and recent nonconventional, bioinspired, methods for the aqueous synthesis of colloidal semiconductor quantum dots (QDs). The basic chemistry concepts are critically emphasized at the very beginning as these are strongly correlated with the selection of ligands and the optimal formation of aqueous QDs and their more sophisticated structures. The synergies of biomimetic and biosynthetic methods that can combine biospecific reactivity with the robust and strong optical responses of QDs have also resulted in new approaches to the synthesis of the nanoparticles themselves. A related new avenue is the recent extension of QD synthesis to form nanoparticles endowed with chiral optical properties. The optical characteristics of QD materials and their advanced forms such as core/shell heterostructures, alloys, and doped QDs are discussed: from the design considerations of optical band gap tuning, the control and reduction of the impact of surface traps, the consideration of charge carrier processes that affect emission and energy and charge transfer, to the impact and influence of lattice strain. We also describe the considerable progress in some selected QD applications such as in bioimaging and theranostics. The review concludes with future strategies and identification of key challenges that still need to be resolved in reaching very attractive, scalable, yet versatile aqueous syntheses that may widen the scope of commercial applications for semiconductor nanocrystals.

Kanehira, T., T. Matsuura, et al. "Impact of Real-Time Image Gating on Spot Scanning Proton Therapy for Lung Tumors: A Simulation Study." Int J Radiat Oncol Biol Phys. 2017 Jan 1;97(1):173-181. doi: 10.1016/j.ijrobp.2016.09.027. Epub 2016 Sep 28.

PURPOSE: To investigate the effectiveness of real-time-image gated proton beam therapy for lung tumors and to establish a suitable size for the gating window (GW). METHODS AND MATERIALS: A proton beam gated by a fiducial marker entering a preassigned GW (as monitored by 2 fluoroscopy units) was used with 7 lung cancer patients. Seven treatment plans were generated: real-time-image gated proton beam therapy with GW sizes of +/-1, 2, 3, 4, 5, and 8 mm and free-breathing proton therapy. The prescribed dose was 70 Gy (relative biological effectiveness)/10 fractions to 99% of the target. Each of the 3-dimensional marker positions in the time series was associated with the appropriate 4-dimensional computed tomography phase. The 4-dimensional dose calculations were performed. The dose distribution in each respiratory phase was deformed into the end-exhale computed tomography image. The D99 and D5 to D95 of the clinical target volume scaled by the prescribed dose with criteria of D99 >95% and D5 to D95 <5%, V20 for the normal lung, and treatment times were evaluated. RESULTS: Gating windows </= +/-2 mm fulfilled the CTV criteria for all patients (whereas the criteria were not always met for GWs >/= +/-3 mm) and gave an average reduction in V20 of more than 17.2% relative to free-breathing proton therapy (whereas GWs >/= +/-4 mm resulted in similar or increased V20). The average (maximum) irradiation times were 384 seconds (818 seconds) for the +/-1-mm GW, but less than 226 seconds (292 seconds) for the +/-2-mm GW. The maximum increased considerably at +/-1-mm GW. CONCLUSION: Real-time-image gated proton beam therapy with a GW of +/-2 mm was demonstrated to be suitable, providing good dose distribution without greatly extending treatment time.

Katari, S. K., P. Natarajan, et al. "Inhibitor design against JNK1 through e-pharmacophore modeling docking and molecular dynamics simulations." J Recept Signal Transduct Res. 2016 Dec;36(6):558-571. Epub 2016 Feb 24.

c-Jun-NH2 terminal kinases (JNKs) come under a class of serine/threonine protein kinases and are encoded by three genes, namely JNK1, JNK2 and JNK3. Human JNK1 is a cytosolic kinase belonging to mitogen-activated protein kinase (MAPK) family, which plays a major role in intracrinal signal transduction cascade mechanism. Overexpressed human JNK1, a key kinase interacts with other kinases involved in the etiology of many cancers, such as skin cancer, liver cancer, breast cancer, brain tumors, leukemia, multiple myeloma and lymphoma. Thus, to unveil a novel human JNK1 antagonist, receptor-based pharmacophore modeling was performed with the available eighteen cocrystal structures of JNK1 in the protein data bank. Eighteen e-pharmacophores were generated from the 18 cocrystal structures. Four common e-pharmacophores were developed from the 18 e-pharmacophores, which were used as three-dimensional (3D) query for shape-based similarity screening against more than one million small molecules to generate a JNK1 ligand library. Rigid receptor docking (RRD) performed using GLIDE v6.3 for the 1683 compounds from in-house library and 18 cocrystal ligands with human JNK1 from lower stringency to higher stringency revealed 17 leads. Further to derive the best leads, dock complexes obtained from RRD were studied further with quantum-polarized ligand docking (QPLD), induced fit docking (IFD) and molecular

mechanics/generalized Born surface area (MM-GBSA). Four leads have showed lesser binding free energy and better binding affinity towards JNK1 compared to 18 cocrystal ligands. Additionally, JNK1-lead1 complex interaction stability was reasserted using 50 ns MD simulations run and also compared with the best resolute cocrystal structure using Desmond v3.8. Thus, the results obtained from RRD, QPLD, IFD and MD simulations indicated that lead1 might be used as a potent antagonist toward human JNK1 in cancer therapeutics.

Katoh, N., I. Soda, et al. "Clinical outcomes of stage I and IIA non-small cell lung cancer patients treated with stereotactic body radiotherapy using a real-time tumor-tracking radiotherapy system." Radiat Oncol. 2017 Jan 5;12(1):3. doi: 10.1186/s13014-016-0742-3.

PURPOSE: To investigate the clinical outcomes of stage I and IIA non-small cell lung cancer (NSCLC) patients treated with stereotactic body radiotherapy (SBRT) using a real-time tumor-tracking radiotherapy (RTRT) system. MATERIALS AND METHODS: Patterns-of-care in SBRT using RTRT for histologically proven, peripherally located, stage I and IIA NSCLC was retrospectively investigated in four institutions by an identical clinical report format. Patterns-of-outcomes was also investigated in the same manner. RESULTS: From September 2000 to April 2012, 283 patients with 286 tumors were identified. The median age was 78 years (52-90) and the maximum tumor diameters were 9 to 65 mm with a median of 24 mm. The calculated biologically effective dose (10) at the isocenter using the linear-quadratic model was from 66 Gy to 126 Gy with a median of 106 Gy. With a median follow-up period of 28 months (range 0-127), the overall survival rate for the entire group, for stage IA, and for stage IB + IIA was 75%, 79%, and 65% at 2 years, and 64%, 70%, and 50% at 3 years, respectively. In the multivariate analysis, the favorable predictive factor was female for overall survival. There were no differences between the clinical outcomes at the four institutions. Grade 2, 3, 4, and 5 radiation pneumonitis was experienced by 29 (10.2%), 9 (3.2%), 0, and 0 patients. The subgroup analyses revealed that compared to margins from gross tumor volume (GTV) to planning target volume (PTV) >/= 10 mm, margins < 10 mm did not worsen the overall survival and local control rates, while reducing the risk of radiation pneumonitis. CONCLUSIONS: This multi-institutional retrospective study showed that the results were consistent with the recent patterns-of-care and patterns-of-outcome analysis of SBRT. A prospective study will be required to evaluate SBRT using a RTRT system with margins from GTV to PTV < 10mm.

Keisham, B., A. Cole, et al. "Cancer Cell Hyperactivity and Membrane Dipolarity Monitoring via Raman Mapping of Interfaced Graphene: Toward Non-Invasive Cancer Diagnostics." ACS Appl Mater Interfaces. 2016 Dec 7;8(48):32717-32722. Epub 2016 Nov 22.

Ultrasensitive detection, mapping, and monitoring of the activity of cancer cells is critical for treatment evaluation and patient care. Here, we demonstrate that a cancer cell's glycolysis-induced hyperactivity and enhanced electronegative membrane (from sialic acid) can sensitively modify the second-order overtone of in-plane phonon vibration energies (2D) of interfaced graphene via a hole-doping mechanism. By leveraging ultrathin graphene's high quantum capacitance and responsive phononics, we sensitively differentiated the activity of interfaced Glioblastoma Multiforme (GBM) cells, a malignant brain tumor, from that of human astrocytes at a single-cell resolution. GBM cell's high surface electronegativity (potential approximately 310 mV) and hyperacidic-release induces hole-doping in graphene with a 3-fold higher 2D vibration energy shift of approximately 6 +/- 0.5 cm-1 than astrocytes. From molecular dipole-induced quantum coupling, we estimate that the sialic acid density on the cell membrane increases from one molecule per approximately 17 nm2 to one molecule per approximately 7 nm2. Furthermore, graphene phononic response also identified enhanced acidity of cancer cell's growth medium. Graphene's phonon-sensitive platform to determine interfaced cell's activity/chemistry will potentially open avenues for studying activity of other cancer cell types, including metastatic tumors, and characterizing different grades of their malignancy.

Kim, E. H., M. S. Kim, et al. "Metformin enhances the radiosensitivity of human liver cancer cells to gamma-rays and carbon ion beams." Oncotarget. 2016 Dec 6;7(49):80568-80578. doi: 10.18632/oncotarget.12966.

The purpose of this study was to investigate the effect of metformin on the responses of hepatocellular carcinoma (HCC) cells to gamma-rays (low-linear energy transfer (LET) radiation) and carbon-ion beams (high-LET radiation). HCC cells were pretreated with metformin and exposed to a single dose of gamma-rays or carbon ion beams. Metformin treatment increased radiation-induced clonogenic cell death, DNA damage, and apoptosis. Carbon ion beams combined with metformin were more effective than carbon ion beams or gamma-rays alone at inducing subG1 and decreasing G2/M arrest, reducing the expression of vimentin, enhancing phospho-AMPK expression, and suppressing phospho-mTOR and phospho-Akt. Thus, metformin effectively

enhanced the therapeutic effect of radiation with a wide range of LET, in particular carbon ion beams and it may be useful for increasing the clinical efficacy of carbon ion beams.

Kim, M. M., R. Penjweini, et al. "A Comparison of Singlet Oxygen Explicit Dosimetry (SOED) and Singlet Oxygen Luminescence Dosimetry (SOLD) for Photofrin-Mediated Photodynamic Therapy." Cancers (Basel). 2016 Dec 6;8(12). pii: E109.

Accurate photodynamic therapy (PDT) dosimetry is critical for the use of PDT in the treatment of malignant and nonmalignant localized diseases. A singlet oxygen explicit dosimetry (SOED) model has been developed for in vivo purposes. It involves the measurement of the key components in PDT-light fluence (rate), photosensitizer concentration, and ground-state oxygen concentration ([(3)O(2)])-to calculate the amount of reacted singlet oxygen ([(1)O(2)]rx), the main cytotoxic component in type II PDT. Experiments were performed in phantoms with the photosensitizer Photofrin and in solution using phosphorescence-based singlet oxygen luminescence dosimetry (SOLD) to validate the SOED model. Oxygen concentration and photosensitizer photobleaching versus time were measured during PDT, along with direct SOLD measurements of singlet oxygen and triplet state lifetime (tauDelta and taut), for various photosensitizer concentrations to determine necessary photophysical parameters. SOLD-determined cumulative [(1)O(2)]rx was compared to SOED-calculated [(1)O(2)]rx for various photosensitizer concentrations to show a clear correlation between the two methods. This illustrates that explicit dosimetry can be used when phosphorescence-based dosimetry is not feasible. Using SOED modeling, we have also shown evidence that SOLD-measured [(1)O(2)]rx using a 523 nm pulsed laser can be used to correlate to singlet oxygen generated by a 630 nm laser during a clinical malignant pleural mesothelioma (MPM) PDT protocol by using a conversion formula.

Koike, M., Y. Yutoku, et al. "Cloning, localization and focus formation at DNA damage sites of canine XLF." J Vet Med Sci. 2016 Oct 14.

Understanding the molecular mechanisms of DNA double-strand break (DSB) repair processes, especially nonhomologous DNA-end joining (NHEJ), is critical for developing next-generation radiotherapies and chemotherapeutics for human and animal cancers. The localization, protein-protein interactions and post-translational modifications of core NHEJ factors, such as human Ku70 and Ku80, might play critical roles in controlling NHEJ activity. XRCC4-like factor (XLF) is a core NHEJ factor and plays a key role in the Ku-dependent NHEJ repair process in human cells. Recently, companion animals, such as canines, have been proposed to be a good model for many aspects of cancer research, including the development of chemotherapeutics. However, the localization and regulation of core NHEJ factors in canine cells have not been elucidated. Here, we show that the localization of canine XLF changes dynamically during the cell cycle. EYFP-canine XLF localizes in the nuclei of interphase cells and accumulates immediately at microirradiated DSB sites. The structure of a putative human XLF nuclear localization signal (NLS) and a putative 14-3-3 binding motif are evolutionarily conserved in canine, chimpanzee and mouse XLF. However, the putative beta-TRCP-recognizable degron of human XLF is not conserved in canine and mouse. Additionally, some vital human XLF phosphorylation sites, including the ATM major phosphorylation site (S251), are not conserved in canine XLF. Our findings might be useful for the study of the molecular mechanisms of NHEJ in canine cells and for the development of new radiosensitizers that target XLF.

Koike, M., Y. Yutoku, et al. "Cloning, localization and focus formation at DNA damage sites of canine XRCC4." J Vet Med Sci. 2017 Jan 10;78(12):1865-1871. doi: 10.1292/jvms.16-0381. Epub 2016 Sep 18.

Various chemotherapies and radiation therapies are useful for killing cancer cells mainly by inducing DNA double-strand breaks (DSBs). Uncovering the molecular mechanisms of DSB repair processes is crucial for developing next-generation radiotherapies and chemotherapeutics for human and animal cancers. XRCC4 plays a critical role in Ku-dependent nonhomologous DNA-end joining (NHEJ) in human cells, and is one of the core NHEJ factors. The localization of core NHEJ factors, such as human Ku70 and Ku80, might play a crucial role in regulating NHEJ activity. Recently, companion animals, such as canines, have been proposed to be a good model in many aspects of cancer research. However, the localization and regulation mechanisms of core NHEJ factors in canine cells have not been elucidated. Here, we show that the expression and subcellular localization of canine XRCC4 changes dynamically during the cell cycle. Furthermore, EYFP-canine XRCC4 accumulates quickly at laser-microirradiated DSB sites. The structure of a putative human XRCC4 nuclear localization signal (NLS) is highly conserved in canine, chimpanzee and mouse XRCC4. However, the amino acid residue corresponding to the human XRCC4 K210, thought to be important for nuclear localization, is not conserved in canine XRCC4. Our findings might be useful for the study of the molecular mechanisms of Ku-dependent NHEJ in canine cells

and the development of new radiosensitizers that target XRCC4.

Kominkova, M., V. Milosavljevic, et al. "Comparative study on toxicity of extracellularly biosynthesized and laboratory synthesized CdTe quantum dots." J Biotechnol. 2017 Jan 10;241:193-200. doi: 10.1016/j.jbiotec.2016.10.024. Epub 2016 Oct 29.

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.

Komiya, Y., Y. Onodera, et al. "The Rho guanine nucleotide exchange factor ARHGEF5 promotes tumor malignancy via epithelial-mesenchymal transition." Oncogenesis. 2016 Sep 12;5(9):e258. doi: 10.1038/oncsis.2016.59.

Epithelial tumor cells often acquire malignant properties, such as invasion/metastasis and uncontrolled cell growth, by undergoing epithelial-mesenchymal transition (EMT). However, the mechanisms by which EMT contributes to malignant progression remain elusive. Here we show that the Rho guanine nucleotide exchange factor (GEF) ARHGEF5 promotes tumor malignancy in a manner dependent on EMT status. We previously identified ARHGEF5, a member of the Dbl family of GEFs, as a multifunctional mediator of Src-induced cell invasion and tumor growth. In the present study, ARHGEF5 was upregulated during tumor growth factor-beta-induced EMT in human epithelial MCF10A cells, and promoted cell migration by activating the Rho-ROCK pathway. ARHGEF5 was necessary for the invasive and in vivo metastatic activity of human colorectal cancer HCT116 cells. These findings underscore the crucial role of ARHGEF5 in cell migration and invasion/metastasis. An in vivo tumorigenesis assay revealed that ARHGEF5 had the potential to promote tumor growth via the phosphatidylinositol 3-kinase (PI3K) pathway. However, ARHGEF5 was not required for tumor growth in epithelial-like human colorectal cancer HCT116 and HT29 cells, whereas the growth of mesenchymal-like SW480 and SW620 cells depended on ARHGEF5. Induction of EMT by tumor necrosis factor-alpha or Slug in HCT116 cells resulted in the dependence of tumor growth on ARHGEF5. In these mesenchymal-like cells, Akt was activated via ARHGEF5 and its activity was required for tumor growth. Analysis of a transcriptome data set revealed that the combination of ARHGEF5 upregulation and E-cadherin downregulation or Snail upregulation was significantly correlated with poor prognosis in patients with colorectal cancers. Taken together, our findings suggest that EMT-induced ARHGEF5 activation contributes to the progression of tumor malignancy. ARHGEF5 may serve as a potential therapeutic target in a subset of malignant tumors that have undergone EMT.

Kong, M., L. Liu, et al. "Single-Molecule Imaging Reveals that Rad4 Employs a Dynamic DNA Damage Recognition Process." Mol Cell. 2016 Oct 20;64(2):376-387. doi: 10.1016/j.molcel.2016.09.005. Epub 2016 Oct 6.

Nucleotide excision repair (NER) is an evolutionarily conserved mechanism that processes helix-destabilizing and/or -distorting DNA lesions, such as UV-induced photoproducts. Here, we investigate the dynamic protein-DNA interactions during the damage recognition step using single-molecule fluorescence microscopy. Quantum dot-labeled Rad4-Rad23 (yeast XPC-RAD23B ortholog) forms non-motile complexes or conducts a one-dimensional search via either random diffusion or constrained motion. Atomic force microcopy analysis of Rad4 with the beta-hairpin domain 3 (BHD3) deleted reveals that this motif is non-essential for damage-specific binding and DNA bending. Furthermore, we find that deletion of seven residues in the tip of beta-hairpin in BHD3 increases Rad4-Rad23 constrained motion at the expense of stable binding at sites of DNA lesions, without diminishing cellular UV resistance or photoproduct repair in vivo. These results suggest a distinct intermediate in the damage recognition process during NER, allowing dynamic DNA damage detection at a distance.

Kulkarni, A., S. K. Natarajan, et al. "Combining Immune Checkpoint Inhibitors and Kinase-Inhibiting Supramolecular Therapeutics for Enhanced Anticancer Efficacy." ACS Nano. 2016 Sep 29.

A major limitation of immune checkpoint

inhibitors is that only a small subset of patients achieve durable clinical responses. This necessitates the development of combinatorial regimens with immunotherapy. However, some combinations, such as MEK- or PI3K-inhibitors with a PD1-PDL1 checkpoint inhibitor, are pharmacologically challenging to implement. We rationalized that such combinations can be enabled using nanoscale supramolecular targeted therapeutics, which spatially home into tumors and exert temporally sustained inhibition of the target. Here we describe two case studies where nanoscale MEK- and PI3K-targeting supramolecular therapeutics were engineered using a quantum mechanical all-atomistic simulation-based approach. The combinations of nanoscale MEK- and PI3K-targeting supramolecular therapeutics with checkpoint PDL1 and PD1 inhibitors exert enhanced antitumor outcome in melanoma and breast cancers in vivo, respectively. Additionally, the temporal sequence of administration impacts the outcome. The combination of supramolecular therapeutics and immunotherapy could emerge as a paradigm shift in the treatment of cancer.

Kulkarni, A., P. Pandey, et al. "Algorithm for Designing Nanoscale Supramolecular Therapeutics with Increased Anticancer Efficacy." ACS Nano. 2016 Sep 27;10(9):8154-68. doi: 10.1021/acsnano.6b00241. Epub 2016 Jul 29.

In the chemical world, evolution is mirrored in the origin of nanoscale supramolecular structures from molecular subunits. The complexity of function acquired in a supramolecular system over a molecular subunit can be harnessed in the treatment of cancer. However, the design of supramolecular nanostructures is hindered by a limited atomistic level understanding of interactions between building blocks. Here, we report the development of a computational algorithm, which we term Volvox after the first multicellular organism, that sequentially integrates quantum mechanical energy-state- and force-field-based models with large-scale all-atomistic explicit water molecular dynamics simulations to design stable nanoscale lipidic supramolecular structures. In one example, we demonstrate that Volvox enables the design of a nanoscale taxane supramolecular therapeutic. In another example, we demonstrate that Volvox can be extended to optimizing the ratio of excipients to form a stable nanoscale supramolecular therapeutic. The nanoscale taxane supramolecular therapeutic exerts greater antitumor efficacy than a clinically used taxane in vivo. Volvox can emerge as a powerful tool in the design of nanoscale supramolecular therapeutics for effective treatment of cancer.

Kumar, S., K. Boone, et al. "Possible existence of optical communication channels in the brain." Sci Rep. 2016 Nov 7;6:36508. doi: 10.1038/srep36508.

Given that many fundamental questions in neuroscience are still open, it seems pertinent to explore whether the brain might use other physical modalities than the ones that have been discovered so far. In particular it is well established that neurons can emit photons, which prompts the question whether these biophotons could serve as signals between neurons, in addition to the well-known electro-chemical signals. For such communication to be targeted, the photons would need to travel in waveguides. Here we show, based on detailed theoretical modeling, that myelinated axons could serve as photonic waveguides, taking into account realistic optical imperfections. We propose experiments, both in vivo and in vitro, to test our hypothesis. We discuss the implications of our results, including the question whether photons could mediate long-range quantum entanglement in the brain.

Labas, A., B. Kramos, et al. "Combined Docking and Quantum Chemical Study on CYP-Mediated Metabolism of Estrogens in Man." Chem Res Toxicol. 2016 Dec 14.

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., C. C. Huang, et al. "Aqueous synthesis of Ag and Mn co-doped In2S3/ZnS quantum dots with tunable emission for dual-modal targeted imaging." Acta Biomater. 2016 Dec 18. pii: S1742-7061(16)30696-1. doi: 10.1016/j.actbio.2016.12.028.

Here, we present the microwave-assisted synthesis of In2S3/ZnS core/shell quantum dots (QDs) co-doped with Ag+ and Mn2+ (referred to as AgMn:In2S3/ZnS). Ag+ altered the optical properties of the host QDs, whereas the spin magnetic moment (S=5/2) of Mn2+ 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:In2S3/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-1mM-1), and robust photostability. In addition, they exhibited excellent stability over a wide pH range (5-12) and high ionic strength (0.15-2.0M NaCl). As seen by confocal microscopy and magnetic resonance imaging, AgMn:In2S3/ZnS conjugated to hyaluronic acid (referred to as AgMn:In2S3/ZnS@HA) efficiently and specifically targeted cluster determinant 44, a receptor overexpressed on cancer cells. Moreover, AgMn:In2S3/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 In2S3/ZnS core/shell quantum dots (QDs) co-doped with Ag+ and Mn2+ (referred to as AgMn:In2S3/ZnS). Ag+ dopants were used to alter the optical properties of the In2S3 host, whereas Mn2+ 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 500mug/mL AgMn:In2S3/ZnS@HA did not cause obvious toxicity to zebrafish embryos. In vitro targeted cell luminescence and magnetic resonance imaging showed that AgMn:In2S3/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.

Li, J., Y. Wang, et al. "Effective combination treatment of lung cancer cells by single vehicular delivery of siRNA and different anticancer drugs." Int J Nanomedicine. 2016 Sep 13;11:4609-4624. eCollection 2016.

In recent years, lung cancer has become one of the fastest growing cancers in the world. Thus, the development of efficient combination therapy to treat lung cancer has attracted significant attention in the cancer therapy field. In this article, we developed a single vehicle drug delivery system, based on quantum dot (QD) nanoparticles, to deliver small interfering RNA (siRNA; target Bcl-2) and different anticancer drugs (carboplatin, paclitaxel, and doxorubicin) simultaneously for treating A549 lung cancer cells efficiently by combination therapy. The QD nanoparticles were conjugated with l-arginine (l-Arg) and different kinds of hydroxypropyl-cyclodextrins (HP-alpha-CDs, HP-beta-CDs, and HP-gamma-CDs) on the surface to form the delivery nanocarriers (QD nanocarriers). They were able to not only bind and transport the siRNA through electrostatic interactions with l-Arg residues but also accommodate various disparate anticancer drugs using different HP-CD modifications. Compared with free drug treatments, the use of QD nanocarriers to deliver Bcl-2 siRNA and different anticancer drugs simultaneously exerted a threefold to fourfold increase in cytotoxicity in A549 cells, which greatly improved the treatment efficacy through combined action. Furthermore, the QD nanocarriers could be used as a probe for real-time imaging of the drug delivery and release because of their strong fluorescence properties. These findings indicate that multifunctional QD nanocarriers hold great promise as a powerful tool for combination therapy for lung cancer.

Li, Z., X. He, et al. "DNA-Programmed Quantum Dot Polymerization for Ultrasensitive Molecular Imaging of Cancer Cells." Anal Chem. 2016 Oct 4;88(19):9355-9358. Epub 2016 Sep 22.

Inorganic nanocrystals, such as quantum dots (QDs), hold great promise as molecular imaging contrast agents because of their superior optical properties. However, the molecular imaging sensitivity of these probes is far from optimized due to the lack of efficient and general method for molecular engineering of nanocrystal into effective bioprobes for signal-amplified imaging. Herein, we develop a strategy to boost the molecular imaging sensitivity of QDs over the limit by copolymerizing QDs and cell-binding aptamers into linear QD-aptamer polymers (QAPs) through DNA-programmed hybridization chain reaction. We show that the cancer cells treated with QAPs exhibit much stronger photoluminescence (PL) signal than those treated with QD-aptamer monomers

(QAMs) because of multivalent binding and multi-QD-based signal amplification. The enhanced cell binding and imaging capacity of QAPs significantly improves imaging-based discrimination between different cancer cell types. This approach adds a new dimension for engineering inorganic nanoparticles into effective bioprobes for biomedical applications.

Liang, L., F. Lan, et al. "Fluorescence "turn-on" determination of H2O2 using multilayer porous SiO2/NGQDs and PdAu mimetics enzymatic/oxidative cleavage of single-stranded DNA." Biosens Bioelectron. 2016 Aug 15;82:204-11. doi: 10.1016/j.bios.2016.03.076. Epub 2016 Apr 1.

A 3D microfluidic paper-based fluorescence analytical device with hollow channels based on the turn-on switching of a resonance energy transfer triggered by the *OH induced cleavage of a DNA strand was successfully constructed. And this fluorescent nanoplatform was first designed to achieve in situ and real-time determination of H2O2 released from cancer cells to obtain an accurate determination. With optimal conditions, the proposed method displayed excellent analytical performance for the detection of H2O2 ranging from 0.3 to 1.0mM with a detection limit of 0.1nM. The favorable performances of this sensor were due to the peroxidase-like activity of nitrogen-doped graphene quantum dots (multilayer porous SiO2 act as stabilizer to load more nitrogen-doped graphene quantum dots for signal amplification) and folic acid-pPdAu/GO (which also could act as an efficient fluorescence quencher and a recognition element of cancer cells by folic acid). It was worth noting that it could be used for visually determined the flux of H2O2 from the cells. Therefore, the developed biosensor holds potential for ultrasensitive quantitative analysis of H2O2 and supplies valuable information for diabetes mellitus research and clinical diagnosis.

Liu, F., J. Wang, et al. "Developing a fluorescence-coupled capillary electrophoresis based method to probe interactions between QDs and colorectal cancer targeting peptides." Electrophoresis. 2016 Aug;37(15-16):2170-4. doi: 10.1002/elps.201600165. Epub 2016 May 27.

As is well known, quantum dots (QDs) have become valuable probes for cancer imaging. In particular, QD-labeled targeting peptides are capable of identifying cancer or tumors cells. A new colorectal cancer targeting peptide, cyclo(1, 9)-CTPSPFSHC, has strong targeting ability and also shows great potential in the identification and treatment of colon cancer. Herein, we synthesized a dual functional polypeptide, cyclo(1, 9)-CTPSPFSHCD2 G2 DP9 G3 H6 (H6 -TCP), to investigate its interaction with QDs inside the capillary. Fluorescence-coupled CE was adopted and applied to characterize the self-assembly of H6 -TCP onto QDs. It was indicated that the formation of the assembly was affected by H6 -TCP/QD molar ratio and sampling time. This novel in-capillary assay greatly reduced the sample consumption and the detection time, which was beneficial for the environment. It is expected that this kind of detection method could find more applications to provide more useful information for cancer diagnosis and detection of harm and hazardous substances/organisms in the environment in the future.

Lu, S., G. Li, et al. "Facile and ultrasensitive fluorescence sensor platform for tumor invasive biomaker beta-glucuronidase detection and inhibitor evaluation with carbon quantum dots based on inner-filter effect." Biosens Bioelectron. 2016 Nov 15;85:358-62. doi: 10.1016/j.bios.2016.05.021. Epub 2016 May 6.

Early detection and diagnosis have great practical significances for the effective prevention and treatment of cancer. In this study, we developed a novel, facile and ultra-sensitive fluorescence assay for the determination of tumor invasive biomarker beta-glucuronidase (GLU) based on the inner-filter effect (IFE). The nitrogen-doped carbon quantum dots (N-CQDs) with green photoluminescence were employed as the fluorophore in IFE, and 4-nitrophenyl-beta-D-glucuronide (PNPG) was used to act as GLU substrate, and GLU catalytic product (p-nitrophenol (PNP)) was capable of acting as the robust absorber in IFE to turn off the fluorescence of N-CQDs due to the complementary overlap between the absorption of PNP and the excitation of N-CQDs. Thus, signal of GLU activity could be recorded by the fluorescence intensity of N-CQDs. Unlike other fluorescence sensing mechanism such as fluorescence resonance energy transfer (FRET) or photoinduced electron transfer (PET), IFE has no requirement for electron or energy transfer process or any chemical modification of fluorophore, which makes our assay more flexible and simple. The proposed method exhibited a good linear relationship from 1UL(-1) to 60UL(-1) (R(2)=0.9967) with a low detection limit of 0.3UL(-1). This method was also successfully applied to the analysis of serum samples and the inhibitor screening from natural product. The developed sensor platform was proven to be reliable, facile, sensitive, and selective, making it promising as a candidate for GLU activity detection in clinic tumor diagnose and anti-tumor drug screening.

Luque-Michel, E., E. Imbuluzqueta, et al. "Clinical advances of nanocarrier-based cancer therapy and diagnostics." Expert Opin Drug Deliv. 2017 Jan;14(1):75-92. Epub 2016 Jul 7.

INTRODUCTION: Cancer is a leading cause of death worldwide and efficient new strategies are urgently needed to combat its high mortality and morbidity statistics. Fortunately, over the years, nanotechnology has evolved as a frontrunner in the areas of imaging, diagnostics and therapy, giving the possibility of monitoring, evaluating and individualizing cancer treatments in real-time. Areas covered: Polymer-based nanocarriers have been extensively studied to maximize cancer treatment efficacy and minimize the adverse effects of standard therapeutics. Regarding diagnosis, nanomaterials like quantum dots, iron oxide nanoparticles or gold nanoparticles have been developed to provide rapid, sensitive detection of cancer and, therefore, facilitate early treatment and monitoring of the disease. Therefore, multifunctional nanosystems with both imaging and therapy functionalities bring us a step closer to delivering precision/personalized medicine in the cancer setting. Expert opinion: There are multiple barriers for these new nanosystems to enter the clinic, but it is expected that in the near future, nanocarriers, together with new 'targeted drugs', could replace our current treatments and cancer could become a nonfatal disease with good recovery rates. Joint efforts between scientists, clinicians, the pharmaceutical industry and legislative bodies are needed to bring to fruition the application of nanosystems in the clinical management of cancer.

Ma, B., S. Zhang, et al. "Prolonged fluorescence lifetime of carbon quantum dots by combining with hydroxyapatite nanorods for bio-applications." Nanoscale. 2016 Nov 16.

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.

Ma, Y., Y. Bai, et al. "A panel of promoter methylation markers for invasive and noninvasive early detection of NSCLC using a quantum dots-based FRET approach." Biosens Bioelectron. 2016 Nov 15;85:641-8. doi: 10.1016/j.bios.2016.05.067. Epub 2016 May 24.

Non-small-cell lung cancer (NSCLC) leads to a significant proportion of cancer-related deaths, and early detection of NSCLC can significantly increase cancer survival rates. A promising approach has been studied to exploit DNA methylation, which is closely correlated to early cancer diagnosis. Herein, in order to realize the early detection of NSCLC, we utilized the developed quantum dots-based (QDs-based) fluorescence resonance energy transfer (FRET) nanosensor technique to analyze the promoter methylation in early stage NSCLC tissue samples and noninvasive bronchial brushing specimens. Using this method, the methylation levels can be quantitatively determined by measuring the signal amplification during FRET. A panel of three tumor suppressor genes (PCDHGB6, HOXA9 and RASSF1A) was assessed in 50 paired early stage NSCLC and their adjacent nontumorous tissue (NT) samples, and 50 early stage NSCLC bronchial brushing and normal specimens. The combined detection was able to identify not only tissue samples but noninvasive bronchial brushing specimens from control cases with a high degree of sensitivity of 92% (AUC=0.977, $P<0.001$) and 80% (AUC=0.907, $P<0.001$) respectively, indicating the versatility of promoter expression in invasive and noninvasive NSCLC samples. Therefore this approach can be used to sensitively analyze the methylation levels of cancer-related genes, which might be a potential tool for noninvasive early clinical diagnosis of cancers.

Maity, A. R. and D. Stepensky "Nuclear and perinuclear targeting efficiency of quantum dots depends on density of peptidic targeting residues on their surface." J Control Release. 2016 Dec 29. pii: S0168-3659(16)30811-2. doi: 10.1016/j.jconrel.2016.12.031.

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 quantitate 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.

Malatesti, N., A. Harej, et al. "Synthesis, characterisation and in vitro investigation of photodynamic activity of 5-(4-octadecanamidophenyl)-10,15,20-tris(N-methylpyridinium-3-yl)porphyrin trichloride on HeLa cells using low light fluence rate." Photodiagnosis Photodyn Ther. 2016 Sep;15:115-26. doi: 10.1016/j.pdpdt.2016.07.003. Epub 2016 Jul 16.

Photodynamic therapy (PDT) is a treatment that aims to kill cancer cells by reactive oxygen species, mainly singlet oxygen, produced through light activation of a photosensitiser (PS). Amongst photosensitisers that attracted the most attention in the last decade are cationic and amphiphilic molecules based on porphyrin, chlorin and phthalocyanine structures. Our aim was to join this search for more optimal balance of the lipophilic and hydrophilic moieties in a PS. A new amphiphilic porphyrin, 5-(4-octadecanamidophenyl)-10,15,20-tris(N-methylpyridinium-3-yl)porphyrin trichloride (5) was synthesised and characterised by (1)H NMR, UV-vis and fluorescence spectroscopy, and by MALDI-TOF/TOF spectrometry. In vitro photodynamic activity of 5 was evaluated on HeLa cell lines and compared to the activity of the hydrophilic 5-(4-acetamidophenyl)-10,15,20-tris(N-methylpyridinium-3-yl)porphyrin trichloride (7). Low fluence rate (2mWcm(-2)) of red light (643nm) was used for the activation, and both porphyrins showed a drug dose-response as well as a light dose-response relationship, but the amphiphilic porphyrin was presented with significantly lower IC50 values. The obtained IC50 values for 5 were 1.4muM at 15min irradiation time and 0.7muM when the time of irradiation was 30min, while for 7 these values were 37 and 6 times higher, respectively. These results confirm the importance of the lipophilic component in a PS and show a potential for 5 to be used as a PS in PDT applications.

Mansur, A. A., F. G. de Carvalho, et al. "Carboxymethylcellulose/ZnCdS fluorescent quantum dot nanoconjugates for cancer cell bioimaging." Int J Biol Macromol. 2016 Dec 31;96:675-686. doi: 10.1016/j.ijbiomac.2016.12.078.

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

Mareeswari, P., J. Brijitta, et al. "Rhizopus stolonifer mediated biosynthesis of biocompatible cadmium chalcogenide quantum dots." Enzyme Microb Technol. 2016 Dec;95:225-229. doi: 10.1016/j.enzmictec.2016.08.016. Epub 2016 Aug 31.

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 3x105 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.

McNicholas, K. and M. Z. Michael "Immuno-characterization of Exosomes Using Nanoparticle Tracking Analysis." Methods Mol Biol. 2017;1545:35-42.

Due to their size, small extracellular vesicles such as exosomes have been difficult to identify and to quantify. As the roles that exosomes play in intercellular signalling become clearer, so does their potential utility as both diagnostic biomarkers for disease and as therapeutic vectors. Accurate assessment of exosomes, both their number and their cargo, is important for continued advancement in the field of vesicle research. To that end, several technologies, including nanoparticle tracking analysis, have been developed to define the physical characteristics of vesicle preparations and determine their concentration. This chapter describes a method for identifying the size and concentration of a subpopulation of vesicles in biological samples, using nanoparticle tracking analysis. Characterization of distinct exosomes is enabled by specific marker antibodies, coupled to fluorescent quantum dots.

Mello, J. C., V. W. Moraes, et al. "Enhancement of chlorpromazine antitumor activity by Pluronics F127/L81 nanostructured system against human multidrug resistant leukemia." Pharmacol Res. 2016 Sep;111:102-12. doi: 10.1016/j.phrs.2016.05.032. Epub 2016 Jun 2.

The development of specific tyrosine kinase inhibitors (TKIs) revolutionized the treatment of chronic myeloid leukemia (CML). However, chemoresistance of tumor cells to TKIs has already been described, and several mechanisms account for the multidrug resistance (MDR) phenotypes, including the overexpression of P-glycoprotein (P-gp). This decreases the rate of healing and complete tumor remission. Nanotechnological tools have been studied to allow advances in this field. Poloxamers (Pluronics((R))) have been proposed as drug carriers to improve therapeutic efficacy and decrease side effects, even in cancer therapy, due to their ability to inhibit P-gp. Antipsychotic phenothiazines have been described as potent cytotoxic drugs against several types of tumor cells in vitro. Here, we show that nanostructured micellar systems containing the phenothiazine derivative chlorpromazine (CPZ) potentiated the cytotoxicity of free CPZ and increased the selectivity against CML tumor cells, demonstrating the pharmacological potential of these poloxamer-based nanostructured systems containing CPZ in cancer therapy.

Mendieta-Moreno, J. I., D. G. Trabada, et al. "Quantum Mechanics/Molecular Mechanics Free Energy Maps and Nonadiabatic Simulations for a Photochemical Reaction in DNA: Cyclobutane Thymine Dimer." J Phys Chem Lett. 2016 Nov 3;7(21):4391-4397. Epub 2016 Oct 25.

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.

Mi, P., D. Kokuryo, et al. "A pH-activatable nanoparticle with signal-amplification capabilities for non-invasive imaging of tumour malignancy." Nat Nanotechnol. 2016 Aug;11(8):724-30. doi: 10.1038/nnano.2016.72. Epub 2016 May 16.

Engineered nanoparticles that respond to pathophysiological parameters, such as pH or redox potential, have been developed as contrast agents for the magnetic resonance imaging (MRI) of tumours. However, beyond anatomic assessment, contrast agents that can sense these pathological parameters and rapidly amplify their magnetic resonance signals are desirable because they could potentially be used to monitor the biological processes of tumours and improve cancer diagnosis. Here, we report an MRI contrast agent that rapidly amplifies magnetic

resonance signals in response to pH. We confined Mn(2+) within pH-sensitive calcium phosphate (CaP) nanoparticles comprising a poly(ethylene glycol) shell. At a low pH, such as in solid tumours, the CaP disintegrates and releases Mn(2+) ions. Binding to proteins increases the relaxivity of Mn(2+) and enhances the contrast. We show that these nanoparticles could rapidly and selectively brighten solid tumours, identify hypoxic regions within the tumour mass and detect invisible millimetre-sized metastatic tumours in the liver.

Miyashita, M., K. Gonda, et al. "Quantitative diagnosis of HER2 protein expressing breast cancer by single-particle quantum dot imaging." Cancer Med. 2016 Oct;5(10):2813-2824. doi: 10.1002/cam4.898. Epub 2016 Sep 26.

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.

Mizuno, H., S. Fukuda, et al. "Multicentre dose audit for clinical trials of radiation therapy in Asia." J Radiat Res. 2016 Nov 17.

A dose audit of 16 facilities in 11 countries has been performed within the framework of the Forum for Nuclear Cooperation in Asia (FNCA) quality assurance program. The quality of radiation dosimetry varies because of the large variation in radiation therapy among the participating countries. One of the most important aspects of international multicentre clinical trials is uniformity of absolute dose between centres. The National Institute of Radiological Sciences (NIRS) in Japan has conducted a dose audit of participating countries since 2006 by using radiophotoluminescent glass dosimeters (RGDs). RGDs have been successfully applied to a domestic postal dose audit in Japan. The authors used the same audit system to perform a dose audit of the FNCA countries. The average and standard deviation of the relative deviation between the measured and intended dose among 46 beams was 0.4% and 1.5% (k = 1), respectively. This is an excellent level of uniformity for the multicountry data. However, of the 46 beams measured, a single beam exceeded the permitted tolerance level of +/-5%. We investigated the cause for this and solved the problem. This event highlights the importance of external audits in radiation therapy.

Moore, C. M. and S. S. Taneja "Integrating MRI for the diagnosis of prostate cancer." Curr Opin Urol. 2016 Sep;26(5):466-71. doi: 10.1097/MOU.0000000000000323.

PURPOSE OF REVIEW: We review recent developments in prostate MRI for prostate cancer diagnosis. RECENT FINDINGS: Large series have strengthened the case for the use of MRI prior to subsequent biopsy to maximize the detection of clinically significant disease, and reduce the detection of clinically insignificant disease. This has effectively moved the discussion on from whether MRI is useful in prostate cancer detection to how best to use it, and at which time point. The Prostate Imaging- Reporting And Data System (PIRADS) group have published a second version of the PIRADS criteria for prostate MRI, covering acquisition, interpretation, and reporting both for clinical practice and data collection for research.There is debate about the commonly used and more prescriptive PIRADS system versus the less prescriptive systems based on overall clinical impression of clinically significant disease (e.g. Likert or simplified quantum scoring). Studies suggest that the Likert or simplified quantum scoring approach may outperform PIRADSv2. Published data are conflicting on whether software-assisted fusion of MRI lesions to ultrasound used at biopsy is more effective than visual registration by a trained operator. SUMMARY: The use of prostate MRI is increasing worldwide, and the debate now focuses on how best to use it to optimize the detection of clinically significant disease.

Morikawa, T., M. Koto, et al. "Radiation-induced Parotid Gland Atrophy in Patients with Head and Neck Cancer After Carbon-ion Radiotherapy." Anticancer Res. 2016 Oct;36(10):5403-5407.

This study aimed to clarify the relationship between dosimetric factors and parotid gland (PG) atrophy after carbon ion radiotherapy (C-ion RT). Fifty-four patients with head and neck tumours were enrolled and 93 irradiated PGs were analyzed. Thirty and 24 patients were treated with total doses [relative biological effectiveness (RBE)] of 57.6 Gy and 64.0 Gy, respectively, in 16 fractions. PG volumes were measured using computed tomographic images obtained before C-ion RT and every 3-6 months thereafter. The median follow-up period was 46.4 months (range=24.0-123.0 months). Univariate analysis showed that PG volumes receiving more than 5, 10, 15, and 20 Gy RBE (V5, V10, V15 and V20, respectively), mean dose, and maximum dose were significantly associated with PG atrophy. Multivariate analysis indicated that only V5 was significantly associated with atrophy. Increasing V5 was a significant risk factor for PG atrophy after C-ion RT.

Na, W., Q. Liu, et al. "Highly sensitive detection of acid phosphatase by using a graphene quantum dots-based forster resonance energy transfer." Talanta. 2016 Dec 1;161:469-475. doi: 10.1016/j.talanta.2016.08.043. Epub 2016 Aug 16.

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.

Naganawa, K., M. Koto, et al. "Long-term outcomes after carbon-ion radiotherapy for oral mucosal malignant melanoma." J Radiat Res. 2016 Dec 26. doi: 10.1093/jrr/rrw117.

Oral mucosal malignant melanoma (OMM) is extremely rare and has a poor prognosis. Owing to its rarity, it has not yet been possible to establish an optimal treatment modality. The objective of this study was to evaluate the long-term efficacy of carbon-ion radiotherapy (C-ion RT) for OMM. Between 1997 and 2013, 19 patients with OMM were treated with C-ion RT alone. Patient ages ranged from 44 to 84 years (median, 69 years). Nine men and 10 women were included. OMMs were restaged in accordance with the seventh edition of the tumour/node/metastasis (TNM) Staging System of the International Union Against Cancer. Before treatment, 14 patients had T3 disease and 5 had T4a disease. Three patients were classified as having N1 disease. All patients were classified as having M0. The hard palate was the most frequently involved oral subsite. All patients were treated with 57.6 Gy (relative biological effectiveness) in 16 fractions. The median follow-up period was 61 months (range, 8-190 months). The 5-year local control, overall survival and progression-free survival rates were 89.5%, 57.4% and 51.6%, respectively. For local control and overall survival, T classification was found to be a significant prognostic factor. Grade 2 and 3 osteoradionecrosis was observed in three and four patients, respectively. The presence of teeth within the planning target volume was a significant risk factor for developing osteoradionecrosis. C-ion RT was an effective treatment option with acceptable toxicity for OMM.

Nam, G., S. Rangasamy, et al. "Cell death mechanistic study of photodynamic therapy against breast cancer cells utilizing liposomal delivery of 5,10,15,20-tetrakis(benzo[b]thiophene) porphyrin." J Photochem Photobiol B. 2017 Jan;166:116-125. doi: 10.1016/j.jphotobiol.2016.11.006. Epub 2016 Nov 12.

5,10,15,20-Tetrakis(benzo[b]thiophene) porphyrin (BTP) is a newly synthesized hydrophobic photosensitizer with fluorescence quantum yield in toluene: PhiF=0.062. Previously, its limitations in solubility had hindered scientific experimentation regarding its photodynamic effects on cancer cells. By utilizing various compositions of liposomes in order to alter the solubility of BTP, the photocytotoxicity, reactive oxygen species generation, and subcellular localization of the liposomal BTP were identified in this work. DNA fragmentation and high content screening assays were performed in order to shed light on the tumoricidal mechanism of the liposomal photosensitizer. The MTT assay results showed promising results in the irradiation specific PDT activity against MCF-7 cells in all liposomal compositions. Production of ROS was confirmed in

the liposomal BTP treated MCF-7 cells after irradiation in a concentration dependent manner. The subcellular localization assays revealed that the localization of BTP was dependent on both the photosensitizer's chemical properties and the properties of the delivery agent encapsulating aforesaid substance. Significant DNA fragmentation was observed in both nucleus localizing liposomal BTP, BTP encapsulated DOPC and DOPE (DOPC-BTP and DOPE-BTP), treated MCF-7 cells. All liposomal-BTPs were successful in inducing mitochondrial permeability transition, an increase in the permeability of the mitochondrial membrane, and activating caspase-3/7. ER localizing BTP were able to significantly increase the cytosolic calcium levels by photodynamic therapy, confirming the photodynamic ability of ER localized BTP to damage the ER membrane. The application of liposomes in delivering a novel hydrophobic photosensitizer, BTP, and photodynamic therapy treatment against MCF-7 cells were successful. It was confirmed that the MCF-7 cell death pathway via photodynamic therapy was altered in a controlled manner by controlling the intracellular localization of the photosensitizer through lipid composition adjustment.

Nam, J. S., M. G. Kang, et al. "Endoplasmic Reticulum-Localized Iridium(III) Complexes as Efficient Photodynamic Therapy Agents via Protein Modifications." J Am Chem Soc. 2016 Aug 31;138(34):10968-77. doi: 10.1021/jacs.6b05302. Epub 2016 Aug 22.

Protein inactivation by reactive oxygen species (ROS) such as singlet oxygen ((1)O2) and superoxide radical (O2(*-)) is considered to trigger cell death pathways associated with protein dysfunction; however, the detailed mechanisms and direct involvement in photodynamic therapy (PDT) have not been revealed. Herein, we report Ir(III) complexes designed for ROS generation through a rational strategy to investigate protein modifications by ROS. The Ir(III) complexes are effective as PDT agents at low concentrations with low-energy irradiation (</= 1 J cm(-2)) because of the relatively high (1)O2 quantum yield (> 0.78), even with two-photon activation. Furthermore, two types of protein modifications (protein oxidation and photo-cross-linking) involved in PDT were characterized by mass spectrometry. These modifications were generated primarily in the endoplasmic reticulum and mitochondria, producing a significant effect for cancer cell death. Consequently, we present a plausible biologically applicable PDT modality that utilizes rationally designed photoactivatable Ir(III) complexes.

Ohshima, Y., K. Kaira, et al. "Efficacy of system l amino acid transporter 1 inhibition as a therapeutic target in esophageal squamous cell carcinoma." Cancer Sci. 2016 Oct;107(10):1499-1505. doi: 10.1111/cas.13021. Epub 2016 Oct 3.

System l amino acid transporter 1 (LAT1) is highly expressed in various types of human cancer, and contributes to cancer growth and survival. Recently, we have shown that LAT1 expression is closely related to the growth and aggressiveness of esophageal cancer, and is an independent marker of poor prognosis. However, it remains unclear whether LAT1 inhibition could suppress esophageal cancer growth. In this study, we investigated the tumor-suppressive effects of the inhibition of LAT1. Both LAT1 and CD98, which covalently associates to LAT1 on the membrane, were expressed in human esophageal cancer cell lines KYSE30 and KYSE150. Quantitative PCR analysis showed that the expression of LAT1 was much higher than other subtypes of LAT. A selective inhibitor of LAT, 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH), suppressed cellular uptake of l-14 C-leucine and cell proliferation in a dose-dependent manner. It also suppressed phosphorylation of mammalian target of rapamycin, 4E-BP1, and p70S6K protein, and induced cell cycle arrest at G1 phase. These results suggest that suppression of both mammalian target of rapamycin signaling and cell cycle progression is involved in BCH-induced growth inhibition. In tumor-bearing mice, daily treatment with BCH significantly delayed tumor growth and decreased glucose metabolism, indicating that LAT1 inhibition potentially suppresses esophageal cancer growth in vivo. Thus, our results suggest that LAT1 inhibition could be a promising molecular target for the esophageal cancer therapy.

Ojino, M., S. Yoshida, et al. "First Successful Pre-Distribution of Stable Iodine Tablets Under Japan's New Policy After the Fukushima Daiichi Nuclear Accident." Disaster Med Public Health Prep. 2016 Dec 8:1-5.

Stable iodine tablets are effective in reducing internal exposure to radioactive iodine, which poses a risk for thyroid cancer and other conditions. After the Fukushima Daiichi nuclear power plant accident, the Japanese government shifted its policy on stable iodine tablet distribution from "after-the-fact" to "before-the-fact" and instructed local governments to pre-distribute stable iodine tablets to residents living within a 5-km radius of nuclear facilities. The nation's first pre-distribution of stable iodine tablets was carried out in June and July of 2014 in Kagoshima Prefecture. Health surveys were conducted so that the medication would not be handed out to people with the possibility of side effects. Of the 4715 inhabitants in the area, 132 were found to require a physician's judgment, mostly

to exclude risks of side effects. This was considered important to prevent the misuse of the tablets in the event of a disaster. The importance of collective and individualized risk communication between physicians and inhabitants at the community health level was apparent through this study. Involvement of physicians through the regional Sendai City Medical Association was an important component of the pre-distribution. Physicians of the Sendai City Medical Association were successfully educated by using the Guidebook on Distributing and Administering Stable Iodine Tablets prepared by the Japan Medical Association and Japan Medical Association Research Institute with the collaboration of the National Institute of Radiological Sciences and the Japanese government. Thus, the physicians managed to make decisions on the dispensing of stable iodine tablets according to the health conditions of the inhabitants. All physicians nationwide should be provided continuing medical education on stable iodine tablets. (Disaster Med Public Health Preparedness. 2016;page 1 of 5).

Oksuzoglu, E., T. Ertan-Bolelli, et al. "Antitumor activities on HL-60 human leukemia cell line, molecular docking, and quantum-chemical calculations of some sulfonamide-benzoxazoles." Artif Cells Nanomed Biotechnol. 2016 Nov 10:1-9.

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., Y. Liu, et al. "Near-infrared mediated quantum dots and paclitaxel co-loaded nanostructured lipid carriers for cancer theragnostic." Colloids Surf B Biointerfaces. 2016 Nov 24;150:121-130. doi: 10.1016/j.colsurfb.2016.11.032.

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

Otsuka, Y., H. Sato, et al. "High expression of EPB41L5, an integral component of the Arf6-driven mesenchymal program, correlates with poor prognosis of squamous cell carcinoma of the tongue." Cell Commun Signal. 2016 Nov 21;14(1):28.

BACKGROUND: Squamous cell carcinoma of the tongue (tongue SCC) is a major subtype of head and neck squamous cell carcinoma (HNSCC), which is an intractable cancer under current therapeutics. ARF6 and its effector AMAP1 are often overexpressed in different types of cancers, such as breast cancer and renal cancer, and in these cancers, AMAP1 binds to EPB41L5 to promote invasion, metastasis, and drug resistance. EPB41L5 is a mesenchymal-specific protein, normally induced during epithelial-mesenchymal transition (EMT) to promote focal adhesion dynamics. Similarly to breast cancer and renal cancer, the acquisition of mesenchymal phenotypes is the key process that drives the malignancy of HNSCC. We previously showed that the overexpression of AMAP1 in tongue SCC is statistically correlated with the poor outcome of patients. In this study, we examined whether tongue SCC also expresses EPB41L5 at high levels. RESULTS: Immunohistochemical staining of clinical specimens of tongue SCC demonstrated that high expression levels of EPB41L5 statistically correlate with poor disease-free survival and poor overall

survival rates of patients. The tongue SCC cell line SCC-9, which overexpress Arf6 and AMAP1, also expressed EPB41L5 at high levels to promote invasiveness, whereas the weakly invasive SCC-25 cells did not express EPB41L5 at notable levels. Among the different EMT-associated transcriptional factors, ZEB1 was previously found to be most crucial in inducing EPB41L5 in breast cancer and renal cancer. In contrast, expression levels of ZEB1 did not correlate with the expression levels of EPB41L5 in tongue SCC, whereas KLF8 and FOXO3 levels showed positive correlations with EPB41L5 levels. Moreover, silencing of EPB41L5 only marginally improved the drug resistance of SCC-9 cells, even when coupled with ionizing radiation. CONCLUSION: Our results indicate that activation of the cancer mesenchymal program in tongue SCC, which leads to EPB41L5 expression, closely correlates with the poor prognosis of patients. However, ZEB1 was not the major inducer of EPB41L5 in tongue SCC, unlike in breast cancer and renal cancer. Thus, processes that trigger the mesenchymal program of tongue SCC, which drives their malignancies, seem to be substantially different from those of other cancers.

Padmanabhan, P., A. Kumar, et al. "Nanoparticles in practice for molecular-imaging applications: An overview." Acta Biomater. 2016 Sep 1;41:1-16. doi: 10.1016/j.actbio.2016.06.003. Epub 2016 Jun 2.

Nanoparticles (NPs) are playing a progressively more significant role in multimodal and multifunctional molecular imaging. The agents like Superparamagnetic iron oxide (SPIO), manganese oxide (MnO), gold NPs/nanorods and quantum dots (QDs) possess specific properties like paramagnetism, superparamagnetism, surface plasmon resonance (SPR) and photoluminescence respectively. These specific properties make them able for single/multi-modal and single/multi-functional molecular imaging. NPs generally have nanomolar or micromolar sensitivity range and can be detected via imaging instrumentation. The distinctive characteristics of these NPs make them suitable for imaging, therapy and delivery of drugs. Multifunctional nanoparticles (MNPs) can be produced through either modification of shell or surface or by attaching an affinity ligand to the nanoparticles. They are utilized for targeted imaging by magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), computed tomography (CT), photo acoustic imaging (PAI), two photon or fluorescent imaging and ultra sound etc. Toxicity factor of NPs is also a very important concern and toxic effect should be eliminated. First generation NPs have been designed, developed and tested in living subjects and few of them are already in clinical use. In near future, molecular imaging will get advanced with multimodality and multifunctionality to detect diseases like cancer, neurodegenerative diseases, cardiac diseases, inflammation, stroke, atherosclerosis and many others in their early stages. In the current review, we discussed single/multifunctional nanoparticles along with molecular imaging modalities. STATEMENT OF SIGNIFICANCE: The present article intends to reveal recent avenues for nanomaterials in multimodal and multifunctional molecular imaging through a review of pertinent literatures. The topic emphasises on the distinctive characteristics of nanomaterial which makes them, suitable for biomedical imaging, therapy and delivery of drugs. This review is more informative of indicative technologies which will be helpful in a way to plan, understand and lead the nanotechnology related work.

Perez-Gonzalez, V. H., R. C. Gallo-Villanueva, et al. "Emerging microfluidic devices for cancer cells/biomarkers manipulation and detection." IET Nanobiotechnol. 2016 Oct;10(5):263-275. doi: 10.1049/iet-nbt.2015.0060.

Circulating tumour cells (CTCs) are active participants in the metastasis process and account for approximately 90% of all cancer deaths. As CTCs are admixed with a very large amount of erythrocytes, leukocytes, and platelets in blood, CTCs are very rare, making their isolation, capture, and detection a major technological challenge. Microfluidic technologies have opened-up new opportunities for the screening of blood samples and the detection of CTCs or other important cancer biomarker-proteins. In this study, the authors have reviewed the most recent developments in microfluidic devices for cells/biomarkers manipulation and detection, focusing their attention on immunomagnetic-affinity-based devices, dielectrophoresis-based devices, surface-plasmon-resonance microfluidic sensors, and quantum-dots-based sensors.

Peynshaert, K., S. J. Soenen, et al. "Coating of Quantum Dots strongly defines their effect on lysosomal health and autophagy." Acta Biomater. 2017 Jan 15;48:195-205. doi: 10.1016/j.actbio.2016.10.022. Epub 2016 Oct 17.

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.

Preto, J. "Classical investigation of long-range coherence in biological systems." Chaos. 2016 Dec;26(12):123116. doi: 10.1063/1.4971963.

Almost five decades ago, H. Frohlich [H. Frohlich, "Long-range coherence and energy storage in biological systems," Int. J. Quantum Chem. 2(5), 641-649 (1968)] reported, on a theoretical basis, that the excitation of quantum modes of vibration in contact with a thermal reservoir may lead to steady states, where under high enough rate of energy supply, only specific low-frequency modes of vibration are strongly excited. This nonlinear phenomenon was predicted to occur in biomolecular systems, which are known to exhibit complex vibrational spectral properties, especially in the terahertz frequency domain. However, since the effects of terahertz or lower-frequency modes are mainly classical at physiological temperatures, there are serious doubts that Frohlich's quantum description can be applied to predict such a coherent behavior in a biological environment, as suggested by the author. In addition, a quantum formalism makes the phenomenon hard to investigate using realistic molecular dynamics simulations (MD) as they are usually based on the classical principles. In the current paper, we provide a general classical Hamiltonian description of a nonlinear open system composed of many degrees of freedom (biomolecular structure) excited by an external energy source. It is shown that a coherent behaviour similar to Frohlich's effect is to be expected in the classical case for a given range of parameter values. Thus, the supplied energy is not completely thermalized but stored in a highly ordered fashion. The connection between our Hamiltonian description, carried out in the space of normal modes, and a more standard treatment in the physical space is emphasized in order to facilitate the prediction of the effect from MD simulations. It is shown how such a coherent phenomenon may induce long-range resonance effects that could be of critical importance at the biomolecular level. The present work is motivated by recent experimental evidences of long-lived excited low-frequency modes in protein structures, which were reported as a consequence of the Frohlich's effect.

Przysiecka, L., M. Michalska, et al. "iRGD peptide as effective transporter of CuInZnxS2+x quantum dots into human cancer cells." Colloids Surf B Biointerfaces. 2016 Oct 1;146:9-18. doi: 10.1016/j.colsurfb.2016.05.041. Epub 2016 May 17.

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

normal cells where they were not present. Therefore, iRGD/QD assemblies have a great potential to be used as targeted imaging agents and/or nanocarriers specific to cancer cells.

Radenkovic, D., H. Kobayashi, et al. "Quantum dot nanoparticle for optimization of breast cancer diagnostics and therapy in a clinical setting." Nanomedicine. 2016 Aug;12(6):1581-92. doi: 10.1016/j.nano.2016.02.014. Epub 2016 Mar 22.

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

Ray, B., S. Agarwal, et al. "Deciphering molecular aspects of interaction between anticancer drug mitoxantrone and tRNA." J Biomol Struct Dyn. 2016 Aug 9:1-13.

Mitoxantrone (1,4-dihydroxy-5,8-bis[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedion e) is a synthetically designed antineoplastic agent and structurally similar to classical anthracyclines. It is widely used as a potent chemotherapeutic component against various kinds of cancer and possesses lesser cardio-toxic effects with respect to naturally occurring anthracyclines. In the present study, we have investigated the binding features of mitoxantrone-tRNA complexation at physiological pH using attenuated total reflection-Fourier transform infrared (ATR-FTIR) spectroscopy, circular dichroism (CD) spectroscopy, isothermal titration calorimetry, and UV-visible absorption spectroscopic techniques. FTIR analysis reveals that mitoxantrone interacts mainly with heterocyclic base residues of tRNA along with slight external binding with phosphate-sugar backbone. In particular, mitoxantrone binds at uracil (C=O) and adenine (C=N) sites of biomolecule (tRNA). CD spectroscopic results suggest that there is no major conformational transition in native A-form of tRNA upon mitoxantrone-tRNA adductation except an intensification in the secondary structure of tRNA is evident. The association constant calculated for mitoxantrone-tRNA association is found to be 1.27 x 105 M-1 indicating moderate to strong binding affinity of drug with tRNA. Thermodynamically, mitoxantrone-tRNA interaction is an enthalpy-driven exothermic reaction. Investigation into drug-tRNA interaction can play an essential role in the rational development of RNA targeting chemotherapeutic agents, which also delineate the structural-functional relationship between drug and its target at molecular level.

Ray, B., S. Agarwal, et al. "Structural, conformational and thermodynamic aspects of groove-directed-intercalation of flavopiridol into DNA." J Biomol Struct Dyn. 2016 Nov;34(11):2518-35. doi: 10.1080/07391102.2015.1118708. Epub 2016 Feb 17.

Certain plant-derived alkaloids and flavonoids have shown propitious cytotoxic acitvity against different types of cancer, having deoxyribose nucleic acid (DNA) as their main cellular target. Flavopiridol, a semi-synthetic derivative of rohitukine (a natural compound isolated from Dysoxylum binectariferum plant), has attained much attention owing to its anticancer potential against various haematological malignancies and solid tumours. This work focuses on investigating interaction between flavopiridol and DNA at molecular level in order to decipher its underlying mechanism of action, which is not well understood. To define direct influence of flavopiridol on the structural, conformational and thermodynamic aspects of DNA, various spectroscopic and calorimetric techniques have been used. ATR-FTIR and SERS spectral outcomes indicate a novel insight into groove-directed-intercalation of flavopiridol into DNA via direct binding with nitrogenous bases guanine (C6=O6) and thymine (C2=O2) in DNA groove together with slight external binding to its sugar-phosphate backbone. Circular dichroism spectral analysis of flavopiridol-DNA complexes suggests perturbation in native B-conformation of DNA and its transition into C-form, which may be localized up to a few base pairs of DNA. UV-visible spectroscopic results illustrate dual binding mode of flavopiridol when interacts with DNA having association constant, Ka = 1.18 x 10(4) M(-1). This suggests moderate type of interaction between flavopiridol and DNA. Further, UV melting analysis also supports spectroscopic outcomes. Thermodynamically, flavopiridol-DNA complexation is an enthalpy-driven exothermic process. These conclusions drawn from this study could be helpful in unveiling mechanism of cytoxicity induced by

flavopiridol that can be further applied in the development of flavonoid-based new chemotherapeutics with more specificity and better efficacy.

Rodzik, L., J. Lewandowska-Lancucka, et al. "Novel fluorescent CdTe quantum dot-thymine conjugate-synthesis, properties and possible application." Nanotechnology. 2017 Jan 27;28(4):045701. doi: 10.1088/1361-6528/28/4/045701. Epub 2016 Dec 15.

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 xray 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.

Roosta, S., S. M. Hashemianzadeh, et al. "Encapsulation of cisplatin as an anti-cancer drug into boron-nitride and carbon nanotubes: Molecular simulation and free energy calculation." Mater Sci Eng C Mater Biol Appl. 2016 Oct 1;67:98-103. doi: 10.1016/j.msec.2016.04.100. Epub 2016 Apr 29.

Encapsulation of cisplatin anticancer drug into the single walled (10, 0) carbon nanotube and (10, 0) boron-nitride nanotube was investigated by quantum mechanical calculations and Monte Carlo Simulation in aqueous solution. Solvation free energies and complexation free energies of the cisplatin@ carbon nanotube and cisplatin@ boron-nitride nanotube complexes was determined as well as radial distribution functions of entitled compounds. Solvation free energies of cisplatin@ carbon nanotube and cisplatin@ boron-nitride nanotube were -4.128kcalmol(-1) and -2457.124kcalmol(-1) respectively. The results showed that cisplatin@ boron-nitride nanotube was more soluble species in water. In addition electrostatic contribution of the interaction of boron- nitride nanotube complex and solvent was -281.937kcalmol(-1) which really more than Van der Waals and so the electrostatic interactions play a distinctive role in the solvation free energies of boron- nitride nanotube compounds. On the other hand electrostatic part of the interaction of carbon nanotube complex and solvent were almost the same as Van der Waals contribution. Complexation free energies were also computed to study the stability of related structures and the free energies were negative (-374.082 and -245.766kcalmol(-1)) which confirmed encapsulation of drug into abovementioned nanotubes. However, boron-nitride nanotubes were more appropriate for encapsulation due to their larger solubility in aqueous solution.

Rottmann, J., D. Morf, et al. "A novel EPID design for enhanced contrast and detective quantum efficiency." Phys Med Biol. 2016 Sep 7;61(17):6297-306. doi: 10.1088/0031-9155/61/17/6297. Epub 2016 Aug 5.

Beams-eye-view imaging applications such as real-time soft-tissue motion estimation are hindered by the inherently low image contrast of electronic portal imaging devices (EPID) currently available for clinical use. We introduce and characterize a novel EPID design that provides substantially increased detective quantum efficiency (DQE), contrast-to-noise ratio (CNR) and sensitivity without degradation in spatial resolution. The prototype design features a stack of four conventional EPID layers combined with low noise integrated readout electronics. Each layer consists of a copper plate, a scintillator ([Formula: see text]) and a photodiode/TFT-switch (aSi:H). We characterize the prototype's signal response to a 6 MV photon beam in terms of modulation transfer function (MTF), DQE and CNR. The presampled MTF is estimated using a slanted slit technique, the DQE is calculated from measured normalized noise power spectra (nNPS) and the MTF and CNR is estimated using a Las Vegas contrast phantom. The prototype has been designed and built to be interchangeable with the current clinical EPID on the Varian TrueBeam platform (AS-1200) in terms of size and data output specifications. Performance evaluation is conducted in absolute values as well as in relative terms using the Varian AS-1200 EPID as a reference detector. A fivefold increase of DQE(0) to about 6.7% was observed by using the four-layered design versus the AS-1200 reference detector. No substantial differences are observed between each layer's individual MTF and

the one for all four layers operating combined indicating that defocusing due to beam divergence is negligible. Also, using four layers instead of one increases the signal to noise ratio by a factor of 1.7.

Sahin, B., S. Z. Topal, et al. "Synthesis, Photophysical and Photochemical Properties of a Set of Silicon Phthalocyanines Bearing Anti-Inflammatory Groups." J Fluoresc. 2016 Nov 17.

In this study, a series of novel silicon (IV) phthalocyanines conjugated axially with anti-inflammatory (sulindac) and triethylene glycol groups has been synthesized. Different synthetic strategies were attempted to obtain the targeted molecules in high yield. The compounds were fully characterized by using different analyses techniques. Our objectives were to generate a system with sulindac group which enhances the singlet oxygen generation and exhibits anti-cancer effect. Therefore, photophysical and photochemical properties of these compounds were investigated in different solvents. The substituent effect on fluorescence quantum yield and singlet oxygen generation was evaluated for efficiency in photodynamic therapy (PDT) as photosensitizer. The molecules exhibited no aggregation tendency, solubility in common organic solvents, high singlet oxygen quantum yield and high photostability in DMSO so these favourable properties make them good candidates as photosensitizer for PDT. In addition, their stabilities were investigated in DMSO, THF, acetonitrile and DMF.

Sansalone, L., S. Tang, et al. "Semiconductor Quantum Dots with Photoresponsive Ligands." Top Curr Chem (J). 2016 Oct;374(5):73. Epub 2016 Sep 28.

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., A. Hassanali, et al. "Nuclear quantum effects in a HIV/cancer inhibitor: The case of ellipticine." J Chem Phys. 2016 Nov 28;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.

Sasaki, M. S., S. Endo, et al. "Neutron relative biological effectiveness in Hiroshima and Nagasaki atomic bomb survivors: a critical review." J Radiat Res. 2016 Nov;57(6):583-595. Epub 2016 Sep 10.

The calculated risk of cancer in humans due to radiation exposure is based primarily on long-term follow-up studies, e.g. the life-span study (LSS) on atomic bomb (A-bomb) survivors in Hiroshima and Nagasaki. Since A-bomb radiation consists of a

mixture of gamma-rays and neutrons, it is essential that the relative biological effectiveness (RBE) of neutrons is adequately evaluated if a study is to serve as a reference for cancer risk. However, the relatively small neutron component hampered the direct estimation of RBE in LSS data. To circumvent this problem, several strategies have been attempted, including dose-independent constant RBE, dose-dependent variable RBE, and dependence on the degrees of dominance of intermingled gamma-rays. By surveying the available literature, we tested the chromosomal RBE of neutrons as the biological endpoint for its equivalence to the microdosimetric quantities obtained using a tissue-equivalent proportional counter (TEPC) in various neutron fields. The radiation weighting factor, or quality factor, Qn, of neutrons as expressed in terms of the energy dependence of the maximum RBE, RBEm, was consistent with that predicted by the TEPC data, indicating that the chromosomally measured RBE was independent of the magnitude of coexisting gamma-rays. The obtained neutron RBE, which varied with neutron dose, was confirmed to be the most adequate RBE system in terms of agreement with the cancer incidence in A-bomb survivors, using chromosome aberrations as surrogate markers. With this RBE system, the cancer risk in A-bomb survivors as expressed in unit dose of reference radiation is equally compatible with Hiroshima and Nagasaki cities, and may be potentially applicable in other cases of human radiation exposure.

Sayyadi, N., I. Justiniano, et al. "Sensitive Time-Gated Immunoluminescence Detection of Prostate Cancer Cells Using a TEGylated Europium Ligand." Anal Chem. 2016 Oct 4;88(19):9564-9571. Epub 2016 Sep 15.

We describe the application of a synthetically developed tetradentate beta-diketonate-europium chelate with high quantum yield (39%), for sensitive immunodetection of prostate cancer cells (DU145). MIL38 antibody, a mouse monoclonal antibody against Glypican 1, conjugated directly to the chelate via lysine residues, resulted in soluble (hydrophilic) and stable immunoconjugates. Indirect labeling of the antibody by a europium chelated secondary polyclonal antibody and a streptavidin/biotin pair was also performed. All of these bright luminescent conjugates were used to stain DU145 cells, a prostate cancer cell line, using time gated luminescence microscopy for imaging, and their performances were compared to conventional FITC labeling. For all prepared conjugates, the europium chelate in conjunction with a gated autosynchronous luminescence detector (GALD) completely suppressed the cellular autofluorescence background to allow capture of vivid, high contrast images of immune-stained cancer cells.

Schmuck, E. G., J. M. Koch, et al. "Biodistribution and Clearance of Human Mesenchymal Stem Cells by Quantitative Three-Dimensional Cryo-Imaging After Intravenous Infusion in a Rat Lung Injury Model." Stem Cells Transl Med. 2016 Dec;5(12):1668-1675. Epub 2016 Jul 26.

: Cell tracking is a critical component of the safety and efficacy evaluation of therapeutic cell products. To date, cell-tracking modalities have been hampered by poor resolution, low sensitivity, and inability to track cells beyond the shortterm. Three-dimensional (3D) cryo-imaging coregisters fluorescent and bright-field microcopy images and allows for single-cell quantification within a 3D organ volume. We hypothesized that 3D cryo-imaging could be used to measure cell biodistribution and clearance after intravenous infusion in a rat lung injury model compared with normal rats. A bleomycin lung injury model was established in Sprague-Dawley rats (n = 12). Human mesenchymal stem cells (hMSCs) labeled with QTracker655 were infused via jugular vein. After 2, 4, or 8 days, a second dose of hMSCs labeled with QTracker605 was infused, and animals were euthanized after 60, 120, or 240 minutes. Lungs, liver, spleen, heart, kidney, testis, and intestine were cryopreserved, followed by 3D cryo-imaging of each organ. At 60 minutes, 82% +/- 9.7% of cells were detected; detection decreased to 60% +/- 17% and 66% +/- 22% at 120 and 240 minutes, respectively. At day 2, 0.06% of cells were detected, and this level remained constant at days 4 and 8 postinfusion. At 60, 120, and 240 minutes, 99.7% of detected cells were found in the liver, lungs, and spleen, with cells primarily retained in the liver. This is the first study using 3D cryo-imaging to track hMSCs in a rat lung injury model. hMSCs were retained primarily in the liver, with fewer detected in lungs and spleen. SIGNIFICANCE: Effective bench-to-bedside clinical translation of cellular therapies requires careful understanding of cell fate through tracking. Tracking cells is important to measure cell retention so that delivery methods and cell dose can be optimized and so that biodistribution and clearance can be defined to better understand potential off-target toxicity and redosing strategies. This article demonstrates, for the first time, the use of three-dimensional cryo-imaging for single-cell quantitative tracking of intravenous infused clinical-grade mesenchymal stem cells in a clinically relevant model of lung injury. The important information learned in this study will help guide future clinical and translational stem cell therapies for lung injuries.

Shao, J., H. Xie, et al. "Biodegradable black phosphorus-based nanospheres for in vivo

photothermal cancer therapy." Nat Commun. 2016 Sep 30;7:12967. doi: 10.1038/ncomms12967.

Photothermal therapy (PTT) offers many advantages such as high efficiency and minimal invasiveness, but clinical adoption of PTT nanoagents have been stifled by unresolved concerns such as the biodegradability as well as long-term toxicity. Herein, poly (lactic-co-glycolic acid) (PLGA) loaded with black phosphorus quantum dots (BPQDs) is processed by an emulsion method to produce biodegradable BPQDs/PLGA nanospheres. The hydrophobic PLGA not only isolates the interior BPQDs from oxygen and water to enhance the photothermal stability, but also control the degradation rate of the BPQDs. The in vitro and in vivo experiments demonstrate that the BPQDs/PLGA nanospheres have inappreciable toxicity and good biocompatibility, and possess excellent PTT efficiency and tumour targeting ability as evidenced by highly efficient tumour ablation under near infrared (NIR) laser illumination. These BP-based nanospheres combine biodegradability and biocompatibility with high PTT efficiency, thus promising high clinical potential.

Shen, Y., A. J. Shuhendler, et al. "Two-photon excitation nanoparticles for photodynamic therapy." Chem Soc Rev. 2016 Dec 21;45(24):6725-6741. Epub 2016 Oct 5.

Two-photon excitation (TPE) nanoparticle-based photosensitizers (PSs) that combine the advantages of TPE and nanotechnology have emerged as attractive therapeutic agents for near-infrared red (NIR) light excited photodynamic therapy (PDT) for cancer treatment. TPE PDT is characterized by nonlinear absorption of two relatively low-energy photons of NIR light with the resulting emission of high-energy visible light. This high-energy light can sensitize oxygen to produce cytotoxic reactive oxygen species (ROS) and singlet oxygen (1O2) which can kill cancer cells. The long-wavelength light used to excite TPE NPs allows for deeper tissue penetration to achieve efficient PDT of deep-seated tumors. Moreover, TPE nanoparticles normally have large two-photon absorption (TPA) cross-sections, which hold great potential as efficient two-photon donors in PDT. In this review, we will summarize the recent advances made in the development of TPE nanoparticles for cancer PDT. Five different TPE nanoparticles, including quantum dots (QDs), carbon nanomaterials, silica nanoparticles, gold nanomaterials, and polymer nanoparticles, are summarized in detail, and the existing challenges as well as the future perspectives are also discussed.

Shi, J., J. Lyu, et al. "A fluorescence turn-on biosensor based on graphene quantum dots (GQDs) and molybdenum disulfide (MoS2) nanosheets for epithelial cell adhesion molecule (EpCAM) detection." Biosens Bioelectron. 2016 Sep 4. pii: S0956-5663(16)30884-3. doi: 10.1016/j.bios.2016.09.012.

This paper presents a "turn-on" fluorescence biosensor based on graphene quantum dots (GQDs) and molybdenum disulfide (MoS2) nanosheets for rapid and sensitive detection of epithelial cell adhesion molecule (EpCAM). PEGylated GQDs were used as donor molecules, which could not only largely increase emission intensity but also prevent non-specific adsorption of PEGylated GQD on MoS2 surface. The sensing platform was realized by adsorption of PEGylated GQD labelled EpCAM aptamer onto MoS2 surface via van der Waals force. The fluorescence signal of GQD was then quenched by MoS2 nanosheets via fluorescence resonance energy transfer (FRET) mechanism. In the presence of EpCAM protein, the stronger specific affinity interaction between aptamer and EpCAM protein could detach GQD labelled EpCAM aptamer from MoS2 nanosheets, leading to the restoration of fluorescence intensity. By monitoring the change of fluorescence signal, the target EpCAM protein could be detected sensitively and selectively with a linear detection range from 3nM to 54nM and limit of detection (LOD) around 450pM. In addition, this nanobiosensor has been successfully used for EpCAM-expressed breast cancer MCF-7 cell detection.

Shiba, S., M. Wakatsuki, et al. "Carbon-ion radiotherapy for locally advanced cervical cancer with bladder invasion." J Radiat Res. 2016 Nov;57(6):684-690. Epub 2016 Jul 15.

The purpose of this study was to evaluate the efficacy and toxicities of carbon-ion radiotherapy (C-ion RT) for locally advanced cervical cancer with bladder invasion by a subset analysis of pooled data from eight prospective clinical trials at the National Institute of Radiological Sciences. Between June 1995 and January 2014, 29 patients with locally advanced cervical cancer with bladder invasion were identified. The median age was 56 years old (range 31-79 years old). The median tumor size at diagnosis on magnetic resonance imaging was 6.7 cm (range 3.5-11.0 cm). Histologically, 20 patients had squamous cell carcinoma and 9 had adenocarcinoma. C-ion RT was performed as a dose-escalation study in the initial trials. All patients received prophylactic whole-pelvic or extended-field irradiation and local boost. The total dose to the cervical tumor was 52.8-74.4 Gy (relative biological effectiveness) in 20 or 24 fractions. Weekly cisplatin (40 mg/m2/week, five cycles) was concurrently given to four patients. The median follow-up of all patients was 28.6 months (range 8.8-238.6 months). Grade 2 or higher late complications in

the bladder were observed in eight patients, with seven developing vesicovaginal fistula. Six patients had Grade 2 or higher complications in the rectosigmoid colon. The 3-year overall survival rate was 47%, the 3-year local control rate was 66%, and the 3-year disease-free survival rate was 28%. In this study, C-ion RT showed favorable local control with reasonable toxicities, but the results were still unsatisfactory. We have the expectation of improvement of therapeutic effects by using C-ion RT with concurrent chemotherapy.

Showler, K., M. Nishimura, et al. "Analysis of genes involved in the PI3K/Akt pathway in radiation- and MNU-induced rat mammary carcinomas." J Radiat Res. 2016 Oct 13.

The PI3K/AKT pathway is one of the most important signaling networks in human breast cancer, and since it was potentially implicated in our preliminary investigations of radiation-induced rat mammary carcinomas, our aim here was to verify its role. We included mammary carcinomas induced by the chemical carcinogen 1-methyl-1-nitrosourea to determine whether any changes were radiation-specific. Most carcinomas from both groups showed activation of the PI3K/AKT pathway, but phosphorylation of AKT1 was often heterogeneous and only present in a minority of carcinoma cells. The negative pathway regulator Inpp4b was significantly downregulated in both groups, compared with in normal mammary tissue, and radiation-induced carcinomas also showed a significant decrease in Pten expression, while the chemically induced carcinomas showed a decrease in Pik3r1 and Pdk1. Significant upregulation of the positive regulators Erbb2 and Pik3ca was observed only in chemically induced carcinomas. However, no genes showed clear correlations with AKT phosphorylation levels, except in individual carcinomas. Only rare carcinomas showed mutations in PI3K/AKT pathway genes, yet these carcinomas did not exhibit stronger AKT phosphorylation. Thus, while AKT phosphorylation is a common feature of rat mammary carcinomas induced by radiation or a canonical chemical carcinogen, the mutation of key genes in the pathways or permanent changes to gene expression of particular signaling proteins do not explain the pathway activation in the advanced cancers. Although AKT signaling likely facilitates cancer development and growth in rat mammary carcinomas, it is unlikely that permanent disruption of the PI3K/AKT pathway genes is a major causal event in radiation carcinogenesis.

Singh, S., P. Jha, et al. "A quantum dot-MUC1 aptamer conjugate for targeted delivery of protoporphyrin IX and specific photokilling of cancer cells through ROS generation." Integr Biol (Camb). 2016 Oct 10;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.

Sinha, S., A. P. Kumaran, et al. "Synthesis and cytotoxicity study of novel 3-(triazolyl)coumarins based fluorescent scaffolds." Bioorg Med Chem Lett. 2016 Nov 15;26(22):5557-5561. doi: 10.1016/j.bmcl.2016.09.078. Epub 2016 Oct 1.

Recently a choice of fluorescent bioimaging probes have been developed as medical diagnostic tools. Herein, we have introduced a series of coumarin-based target specific probes for cancer theranostic application which play a dual role in the field of both diagnosis and therapy. A fluorogenic version of 1,3-dipolar cycloaddition between azides and alkynes (DBCO) has been introduced to develop the triazolylcoumarin based fluorescent scaffolds. These scaffolds were screened for their anticancer activity against breast cancer (MCF7) and human epitheloid cervix carcinoma (HeLa) cell line. It was established that triazolylcoumarins (5c and 5d) are having electronegative substitution in the benzene ring displayed most effective anticancer profile in both the cell lines. Compounds 5a and 5d exhibited maximum quantum yield and strong cellular uptake in the MCF-7 cell line.

Son, K., J. S. Kim, et al. "IMAGING DOSE OF HUMAN ORGANS FROM kV-CBCT IN IMAGE-

GUIDED RADIATION THERAPY." Radiat Prot Dosimetry. 2016 Oct 20.

This study investigates dose distribution due to kV cone-beam computed tomography (CBCT) for the patients undergoing CBCT-based image-guided radiation therapy (IGRT). The kV-CBCT provides an efficient image-guidance tool for acquiring the latest volumetric image of a patient's anatomy, and has been being routinely used in clinics for an accurate treatment setup. Imaging radiation doses resulting from six different acquisition protocols of the on-board imager (OBI) were calculated using a Geant4 Application for Tomographic Emission (GATE) Monte Carlo simulation toolkit, and the absorbed doses by various organs were analyzed for the adult and pediatric numerical XCAT phantoms in this study. The calculated organ doses range from 0.1 to 24.1 mGy in the adult phantom, and from 0.1 to 36.8 mGy in the pediatric one. The imaging organ doses to the pediatric phantom turn out to be consistently higher than those to the adult phantom. It is believed that our results would provide reliable data to the clinicians for their making better decisions on CBCT scanning options and would also provide a platform for developing a new kV-CBCT scanning protocol in conjunction with a low-dose capability.

Sonali, R. P. Singh, et al. "RGD-TPGS decorated theranostic liposomes for brain targeted delivery." Colloids Surf B Biointerfaces. 2016 Nov 1;147:129-41. doi: 10.1016/j.colsurfb.2016.07.058. Epub 2016 Jul 29.

The aim of this work was to formulate RGD-TPGS decorated theranostic liposomes, which contain both docetaxel (DTX) and quantum dots (QDs) for brain cancer imaging and therapy. RGD conjugated TPGS (RGD-TPGS) was synthesized and conjugation was confirmed by Fourier transform infrared (FTIR) spectroscopy and electrospray ionisation (ESI) mass spectroscopy (ESI-MS). The theranostic liposomes were prepared by the solvent injection method and characterized for their particle size, polydispersity, zeta-potential, surface morphology, drug encapsulation efficiency, and in-vitro release study. Biocompatibility and safety of theranostic liposomes were studied by reactive oxygen species (ROS) generation study and histopathology of brain. In-vivo study was performed for determination of brain theranostic effects in comparison with marketed formulation (Docel) and free QDs. The particle sizes of the non-targeted and targeted theranostic liposomes were found in between 100 and 200nm. About 70% of drug encapsulation efficiency was achieved with liposomes. The drug release from RGD-TPGS decorated liposomes was sustained for more than 72h with 80% of drug release. The in-vivo results demonstrated that RGD-TPGS decorated theranostic liposomes were 6.47- and 6.98-fold more effective than Docel after 2h and 4h treatments, respectively. Further, RGD-TPGS decorated theranostic liposomes has reduced ROS generation effectively, and did not show any signs of brain damage or edema in brain histopathology. The results of this study have indicated that RGD-TPGS decorated theranostic liposomes are promising carrier for brain theranostics.

Stallivieri, A., L. Colombeau, et al. "Folic acid conjugates with photosensitizers for cancer targeting in photodynamic therapy: Synthesis and photophysical properties." Bioorg Med Chem. 2017 Jan 1;25(1):1-10. doi: 10.1016/j.bmc.2016.10.004. Epub 2016 Oct 10.

Recent researches in photodynamic therapy have focused on novel techniques to enhance tumour targeting of anticancer drugs and photosensitizers. Coupling a photosensitizer with folic acid could allow more effective targeting of folate receptors which are over-expressed on the surface of many tumour cells. In this study, different folic acid-OEG-conjugated photosensitizers were synthesized, characterized and their photophysical properties were evaluated. The introduction of an OEG does not significantly improve the hydrophilicity of the FA-porphyrin. All the FA-targeted photosensitizers present good to very good photophysical properties. The best one appears to be Ce6. Molar extinction coefficient, fluorescence and singlet oxygen quantum yields were determined and were compared to the corresponding photosensitizer alone.

Su, X., C. Chan, et al. "A graphene quantum dot@Fe3O4@SiO2 based nanoprobe for drug delivery sensing and dual-modal fluorescence and MRI imaging in cancer cells." Biosens Bioelectron. 2016 Oct 28. pii: S0956-5663(16)31102-2. doi: 10.1016/j.bios.2016.10.076.

A novel graphene quantum dot (GQD)@Fe3O4@SiO2 based nanoprobe was reported for targeted drug delivery, sensing, dual-modal imaging and therapy. Carboxyl-terminated GQD (C-GQD) was firstly conjugated with Fe3O4@SiO2 and then functionalized with cancer targeting molecule folic acid (FA). DOX drug molecules were then loaded on GQD surface of Fe3O4@SiO2@GQD-FA nanoprobe via pi-pi stacking, which resulted in Fe3O4@SiO2@GQD-FA/DOX conjugates based on a FRET mechanism with GQD as donor molecules and DOX as acceptor molecules. Meanwhile, we successfully performed in vitro MRI and fluorescence imaging of living Hela cells and monitored intracellular drug release process using this Fe3O4@SiO2@GQD-FA/DOX nanoprobe. Cell viability study demonstrated the low cytotoxicity of Fe3O4@SiO2@GQD-FA nanocarrier and the

enhanced therapeutic efficacy of Fe3O4@SiO2@GQD-FA/DOX nanoprobe for cancer cells. This luminomagnetic nanoprobe will be a potential platform for cancer accurate diagnosis and therapy.

Sun, Z., Y. Zhao, et al. "TiL4 -Coordinated Black Phosphorus Quantum Dots as an Efficient Contrast Agent for In Vivo Photoacoustic Imaging of Cancer." Small. 2017 Jan 6. doi: 10.1002/smll.201602896.

Black phosphorus quantum dots coordinated with a sulfonic ester of the titanium ligand are prepared and exhibit enhanced stability. In vitro and in vivo photoacoustic imaging applications demonstrate that the quantum dots can efficiently accumulate inside the tumor producing tumor profiles with high spatial resolution, demonstrating their potential as an efficient agent for photoacoustic imaging.

Tabrizi, L. and H. Chiniforoshan "New RuII pincer complexes: synthesis, characterization and biological evaluation for photodynamic therapy." Dalton Trans. 2016 Nov 15;45(45):18333-18345.

Three new ruthenium(ii) complexes of NCN pincer and phenylcyanamide derivative ligands of the formula [Ru(L)(Ph2phen)(3,5-(NO2)2pcyd)], 1, [Ru(L)(Me2phen)(3,5-(NO2)2pcyd)], 2, and [Ru(L)(Cl2phen)(3,5-(NO2)2pcyd)], 3 (HL: 5-methoxy-1,3-bis(1-methyl-1H-benzo[d]imidazol-2-yl)benzene, 3,5-(NO2)2pcyd: 3,5-(NO2)2pcyd, Ph2phen: 4,7-diphenyl-1,10-phenanthroline, Me2phen: 4,7-dimethyl-1,10-phenanthroline, Cl2phen: 4,7-dichloro-1,10-phenanthroline) have been synthesized and studied as potential photosensitizers (PSs) in photodynamic therapy (PDT). The complexes exhibited promising 1O2 production quantum yields comparable with PSs available on the market. The DNA-binding interactions of the complexes with calf thymus DNA have been studied by absorption, emission, and viscosity measurements. All complexes cleave SC-DNA efficiently on photoactivation at 350 nm with the formation of singlet oxygen (1O2) and hydroxyl radicals (OH) in type-II and photoredox pathways. Complexes 1-3 showed very good uptake in cervical cancer cells (HeLa). The compounds studied were found to exhibit low toxicity against HeLa cells (IC50 > 300 muM) and, remarkably, on non-cancerous MRC-5 cells (IC50 > 100 muM) in the dark. However, 1 showed very promising behavior with an increment of about 90 times, in its cytotoxicity upon light illumination at 420 nm in addition to very good human plasma stability.

Takabatake, M., B. J. Blyth, et al. "DNA Methylation Patterns in Rat Mammary Carcinomas Induced by Pre- and Post-Pubertal Irradiation." PLoS One. 2016 Oct 6;11(10):e0164194. doi: 10.1371/journal.pone.0164194. eCollection 2016.

Several lines of evidence indicate one's age at exposure to radiation strongly modifies the risk of radiation-induced breast cancer. We previously reported that rat mammary carcinomas induced by pre- and post-pubertal irradiation have distinct gene expression patterns, but the changes underlying these differences have not yet been characterized. The aim of this investigation was to see if differences in CpG DNA methylation were responsible for the differences in gene expression between age at exposure groups observed in our previous study. DNA was obtained from the mammary carcinomas arising in female Sprague-Dawley rats that were either untreated or irradiated (gamma-rays, 2 Gy) during the pre- or post-pubertal period (3 or 7 weeks old). The DNA methylation was analyzed using CpG island microarrays and the results compared to the gene expression data from the original study. Global DNA hypomethylation in tumors was accompanied by gene-specific hypermethylation, and occasionally, by unique tumor-specific patterns. We identified methylation-regulated gene expression candidates that distinguished the pre- and post-pubertal irradiation tumors, but these represented only 2 percent of the differentially expressed genes, suggesting that methylation is not a major or primary mechanism underlying the phenotypes. Functional analysis revealed that the candidate methylation-regulated genes were enriched for stem cell differentiation roles, which may be important in mammary cancer development and worth further investigation. However, the heterogeneity of human breast cancer means that the interpretation of molecular and phenotypic differences should be cautious, and take into account the co-variates such as hormone receptor status and cell-of-origin that may influence the associations.

Tamura, M., H. Sakurai, et al. "Lifetime attributable risk of radiation-induced secondary cancer from proton beam therapy compared with that of intensity-modulated X-ray therapy in randomly sampled pediatric cancer patients." J Radiat Res. 2016 Oct 27.

To investigate the amount that radiation-induced secondary cancer would be reduced by using proton beam therapy (PBT) in place of intensity-modulated X-ray therapy (IMXT) in pediatric patients, we analyzed lifetime attributable risk (LAR) as an in silico surrogate marker of the secondary cancer after these treatments. From 242 pediatric patients with cancers who were treated with PBT, 26 patients were selected by random sampling after stratification into four categories: (i) brain, head and neck, (ii) thoracic, (iii) abdominal, and (iv) whole craniospinal (WCNS) irradiation. IMXT was replanned using the same

computed tomography and region of interest. Using the dose-volume histograms (DVHs) of PBT and IMXT, the LARs of Schneider et al were calculated for the same patient. All the published dose-response models were tested for the organs at risk. Calculation of the LARs of PBT and IMXT based on the DVHs was feasible for all patients. The means +/- standard deviations of the cumulative LAR difference between PBT and IMXT for the four categories were (i) 1.02 +/- 0.52% (n = 7, P = 0.0021), (ii) 23.3 +/- 17.2% (n = 8, P = 0.0065), (iii) 16.6 +/- 19.9% (n = 8, P = 0.0497) and (iv) 50.0 +/- 21.1% (n = 3, P = 0.0274), respectively (one tailed t-test). The numbers needed to treat (NNT) were (i) 98.0, (ii) 4.3, (iii) 6.0 and (iv) 2.0 for WCNS, respectively. In pediatric patients who had undergone PBT, the LAR of PBT was significantly lower than the LAR of IMXT estimated by in silico modeling. Although a validation study is required, it is suggested that the LAR would be useful as an in silico surrogate marker of secondary cancer induced by different radiotherapy techniques.

Tang, D., J. Li, et al. "Evaluation of TSPO PET Ligands [18F]VUIIS1009A and [18F]VUIIS1009B: Tracers for Cancer Imaging." Mol Imaging Biol. 2016 Nov 16.

PURPOSE: Positron emission tomography (PET) ligands targeting translocator protein (TSPO) are potential imaging diagnostics of cancer. In this study, we report two novel, high-affinity TSPO PET ligands that are 5,7 regioisomers, [18F]VUIIS1009A ([18F]3A) and [18F]VUIIS1009B ([18F]3B), and their initial in vitro and in vivo evaluation in healthy mice and glioma-bearing rats. PROCEDURES: VUIIS1009A/B was synthesized and confirmed by X-ray crystallography. Interactions between TSPO binding pocket and novel ligands were evaluated and compared with contemporary TSPO ligands using 2D 1H-15N heteronuclear single quantum coherence (HSQC) spectroscopy. In vivo biodistribution of [18F]VUIIS1009A and [18F]VUIIS1009B was carried out in healthy mice with and without radioligand displacement. Dynamic PET imaging data were acquired simultaneously with [18F]VUIIS1009A/B injections in glioma-bearing rats, with binding reversibility and specificity evaluated by radioligand displacement. In vivo radiometabolite analysis was performed using radio-TLC, and quantitative analysis of PET data was performed using metabolite-corrected arterial input functions. Imaging was validated with histology and immunohistochemistry. RESULTS: Both VUIIS1009A (3A) and VUIIS1009B (3B) were found to exhibit exceptional binding affinity to TSPO, with observed IC50 values against PK11195 approximately 500-fold lower than DPA-714. However, HSQC NMR suggested that VUIIS1009A and VUIIS1009B share a common binding pocket within mammalian TSPO (mTSPO) as DPA-714 and to a lesser extent, PK11195. [18F]VUIIS1009A ([18F]3A) and [18F]VUIIS1009B ([18F]3B) exhibited similar biodistribution in healthy mice. In rats bearing C6 gliomas, both [18F]VUIIS1009A and [18F]VUIIS1009B exhibited greater binding potential (k 3/k 4)in tumor tissue compared to [18F]DPA-714. Interestingly, [18F]VUIIS1009B exhibited significantly greater tumor uptake (V T) than [18F]VUIIS1009A, which was attributed primarily to greater plasma-to-tumor extraction efficiency. CONCLUSIONS: The novel PET ligand [18F]VUIIS1009B exhibits promising characteristics for imaging glioma; its superiority over [18F]VUIIS1009A, a regioisomer, appears to be primarily due to improved plasma extraction efficiency. Continued evaluation of [18F]VUIIS1009B as a high-affinity TSPO PET ligand for precision medicine appears warranted.

Tao, L., C. Song, et al. "Anti-CD155 and anti-CD112 monoclonal antibodies conjugated to a fluorescent mesoporous silica nanosensor encapsulating rhodamine 6G and fluorescein for sensitive detection of liver cancer cells." Analyst. 2016 Aug 2;141(16):4933-40. doi: 10.1039/c5an01908g.

A novel method for sensitive detection of liver cancer cells using anti-CD155 and anti-CD112 monoclonal antibodies conjugated to ultrabright fluorescent mesoporous silica nanoparticles (FMSNs) encapsulating Rhodamine 6G and fluorescein was developed. The diameter of the obtained nanoparticles was 90 nm, and the quantum yield was 69%. Because the emission of fluorescein has a high degree of overlap with the excitation of Rhodamine 6G, and these two dyes were sufficiently close to each other on the nanoparticles, fluorescence resonance energy transfer can occur between these two dyes. This transfer not only maintains the original feature of the nanochannels and the skeletal network of the silica weakening the inner filtering of the dye, but also makes the excitation peak of the nanoparticles wider and increases the useful load amount of the dye. Because the wider Stokes shifts weaken the interference of excitation, the detection sensitivity is enhanced at the same time. The NaIO4 oxidation method does not use a cross-linker but rather uses covalent immobilization of the monoclonal antibodies on the FMSNs. This method can maintain the activity of the monoclonal antibodies more easily than the glutaraldehyde method. These advantages ensure that the nanosensor has high sensitivity and specificity for detecting liver cancer SMMC-7721 and HHCC cells. The in vivo imaging experiment also ensured that the biosensor can target tumor tissue in mice.

Thakur, M., A. Mewada, et al. "Milk-derived multi-fluorescent graphene quantum dot-based cancer theranostic system." Mater Sci Eng C Mater Biol Appl. 2016 Oct 1;67:468-77. doi: 10.1016/j.msec.2016.05.007. Epub 2016 May 9.

An economical green-chemistry approach was used for the synthesis of aqueous soluble graphene quantum dots (GQDs) from cow milk for simultaneous imaging and drug delivery in cancer. The GQDs synthesized using one-pot microwave-assisted heating were multi-fluorescent, spherical in shape having a lateral size of ca. 5nm. The role of processing parameters such as heating time and ionic strength showed a profound effect on photoluminescence properties of GQDs. The GQDs were N-doped and oxygen-rich as confirmed by X-ray photoelectron spectroscopy (XPS) analysis. Cysteamine hydrochloride (Cys) was used to attach an anti-cancer drug berberine hydrochloride (BHC) on GQDs forming GQDs@Cys-BHC complex with c.a. 88% drug loading efficiency. In vitro drug release was studied at the acidic-basic environment and drug kinetics was studied using pharmacokinetic statistical models. The GQDs were biocompatible on L929 cells whereas theranostic GQDs@Cys-BHC complex showed a potent cytotoxic effect on different cancerous cell line models: cervical cancer cell lines such as HeLa cells and breast cancer cells such as MDA-MB-231 confirmed by Trypan blue and MTT-based cytotoxic assays. Furthermore, multi-excitation based cellular bioimaging was demonstrated using confocal laser scanning microscopy (CLSM) and fluorescence microscopy using GQDs as well as GQDs@Cys-BHC complex. Thus, drug delivery (therapeutic) and bioimaging (diagnostic) properties of GQDs@Cys-BHC complex are thought to have a potential in vitro theranostic application in cancer therapy.

Thongsak, N., I. Chitapanarux, et al. "Spatial and Temporal Analyses of Cervical Cancer Patients in Upper Northern Thailand." Asian Pac J Cancer Prev. 2016 Nov 1;17(11):5011-5017.

Background: Cervical cancer is a major public health problem worldwide. There have been several studies indicating that risk is associated with geographic location and that the incidence of cervical cancer has changed over time. In Thailand, incidence rates have also been found to be different in each region. Methods: Participants were women living or having lived in upper Northern Thailand and subjected to cervical screening at Maharaj Nakorn Chiang Mai Hospital between January 2010 and December 2014. Generalized additive models with Loess smooth curve fitting were applied to estimate the risk of cervical cancer. For the spatial analysis, Google Maps were employed to find the geographical locations of the participants' addresses. The Quantum Geographic Information System was used to make a map of cervical cancer risk. Two univariate smooths: x equal to the residency duration was used in the temporal analysis of residency duration, and x equal to the calendar year that participants moved to upper Northern Thailand or birth year for participants already living there, were used in the temporal analysis of the earliest year. The spatial-temporal analysis was conducted in the same way as the spatial analysis except that the data were split into overlapping calendar years. Results: In the spatial analysis, the risk of cervical cancer was shown to be highest in the Eastern sector of upper Northern Thailand (p-value <0.001). In the temporal analysis of residency duration, the risk was shown to be steadily increasing (p-value =0.008), and in the temporal analysis of the earliest year, the risk was observed to be steadily decreasing (p-value=0.016). In the spatial-temporal analysis, the risk was stably higher in Chiang Rai and Nan provinces compared to Chiang Mai province. According to the display movement over time, the odds of developing cervical cancer declined in all provinces. Conclusions: The risk of cervical cancer has decreased over time but, in some areas, there is a higher risk than in the major province of Chiang Mai. Therefore, we should promote cervical cancer screening coverage in all areas, especially where access is difficult and/or to women of lower socioeconomic status.

Tsai, H., W. Lin, et al. "Multifunctional nanoparticles for protein detections in thin channels." Biosens Bioelectron. 2017 Apr 15;90:153-158. doi: 10.1016/j.bios.2016.11.023. Epub 2016 Nov 12.

This paper presents a method for simultaneous detection of two proteins by using multifunctional nanoparticles with a magnetic immunoassay in thin channels. Biofunctional magnetic graphene quantum dots (GQDs) combined with two biofunctional quantum dots (QDs) were used for simultaneously detecting two proteins. Magnetic GQDs enabled selective and quantitative nanoparticle deposition with blue emission. Biofunctional QDs confirmed the two protein detections with orange and green emissions. We used two model biomarkers [alpha-fetoprotein (AFP) and cancer antigen 125 (CA125)] to demonstrate the feasibility of the proposed method. The detection limits (0.06pg/mL AFP and 0.001U/mL CA125) and linear ranges (0.2pg/mL-0.68ng/mL AFP and 0.003-25U/mL CA125) of this method are the same as those of single protein detection within experimental errors. These detection limits are substantially lower and the linear ranges are considerably wider than those of enzyme-linked

immunosorbent assay (ELISA) and other immunoassay methods. The differences between the proposed method and an ELISA method in AFP and CA125 measurements of serum samples were less than 12%. The proposed method demonstrates favorable detection of biomarkers with advantages of speed, sensitivity, selectivity, and throughput.

Tsuruoka, C., B. J. Blyth, et al. "Sensitive Detection of Radiation-Induced Medulloblastomas after Acute or Protracted Gamma-Ray Exposures in Ptch1 Heterozygous Mice Using a Radiation-Specific Molecular Signature." Radiat Res. 2016 Oct;186(4):407-414. Epub 2016 Sep 30.

Recently reported studies have led to a heightened awareness of the risks of cancer induced by diagnostic radiological imaging, and in particular, the risk of brain cancer after childhood CT scans. One feature of Ptch1+/- mice is their sensitivity to radiation-induced medulloblastomas (an embryonic cerebellar tumor) during a narrow window of time centered on the days around birth. Little is known about the dynamics of how dose protraction interacts with such narrow windows of sensitivity in individual tissues. Using medulloblastomas from irradiated Ptch1+/- mice with a hybrid C3H x C57BL/6 F1 genetic background, we previously showed that the alleles retained on chromosome 13 (which harbors the Ptch1 gene) reveal two major mechanisms of loss of the wild-type allele. The loss of parental alleles from the telomere extending up to or past the Ptch1 locus by recombination (spontaneous type) accounts for almost all medulloblastomas in nonirradiated mice, while tumors in irradiated mice often exhibited interstitial deletions, which start downstream of the wild-type Ptch1 and extend up varying lengths towards the centromere (radiation type). In this study, Ptch1+/- mice were exposed to an acute dose of either 100 or 500 mGy gamma rays in utero or postnatally, or the same radiation doses protracted over a four-day period, and were monitored for medulloblastoma development. The results showed dose- and age-dependent radiation-induced type tumors. Furthermore, the size of the radiation-induced deletion differed with the dose rate. The results of this work suggest that tumor latency may be related to the size of the deletion. In this study, 500 mGy exposure produced radiation-induced type tumors at all ages and dose rates, while 100 mGy exposure did not significantly produce radiation-induced type tumors. The radiation signature allows for unique mechanistic insight into the action of radiation to induce DNA lesions with known causal relationship to a specific tumor type, particularly for doses and dose rates that are relevant to both diagnostic and accidental radiological exposures.

Tyagi, N., R. De, et al. "Cancer therapeutics with epigallocatechin-3-gallate encapsulated in biopolymeric nanoparticles." Int J Pharm. 2016 Dec 14;518(1-2):220-227. doi: 10.1016/j.ijpharm.2016.12.030.

With the recent quantum leap in chemoprevention by dietary products, their use as cancer therapeutics is garnering worldwide attention. The concept of effortlessly fighting this deadly disease by gulping cups of green tea or swallowing green tea extract capsules is appreciated universally. Epigallocatechin-3-gallate (EGCG), a major polyphenol in green tea, has generated significant interest in controlling carcinogenesis due to its growth-inhibitory efficacy against a variety of cancers by targeting multiple signaling pathways. However, the success of EGCG in preclinical studies is difficult to translate into clinical trials due to issues of low solubility, bioavailability and an uncertain therapeutic window. The laborious and expensive journey of drugs from the laboratory to commercialization can be improved by utilizing nanoparticles as anti-cancer drug carriers. Exploitation of biopolymeric nanoparticles in recent years has improved EGCG's biodistribution, stability and tumor selectivity, revealing its superior chemopreventive effects. This review briefly summarizes recent developments regarding the targets and side effects of EGCG, complications associated with its low bioavailability and critically analyses the application of biopolymeric nanoparticles encapsulating EGCG as a next generation delivery systems.

Vibin, M., R. Vinayakan, et al. "A Novel Fluorescent Quantum Dot Probe for the Rapid Diagnostic High Contrast Imaging of Tumor in Mice." J Fluoresc. 2016 Dec 5.

A simple probe - antibody conjugated silica over coated cadmium selenide quantum dots (QD-Ab probe) for efficient and rapid diagnostic in vivo imaging of tumors is developed. Compared to unconjugated quantum dots (QD), these probes underwent efficient cellular internalization and tumor targeting behavior, retaining bright emission under in vivo cancer models. Silica over coated cadmium selenide quantum dots were conjugated with Epidermal growth factor receptor (EGFR) monoclonal antibody to detect the over expression of EGFR in cancer models. The in vitro cellular internalization efficiency of QD and QD-Ab probe in cultured stem cells (RADMSCs) and cancer cells (HeLa) were assessed by ICP-OES and cLSM. Results demonstrated a greater internalization efficiency of CdSe-Silica QD-Ab probe than CdSe-Silica QDs. For in vivo imaging solid tumor bearing mice was subjected to tail vein injection of QD and QD-Ab

probe. After the specific time interval of injection, mice were anesthetized and subjected into Xenogen IVIS(R)200 imaging system, followed by ex vivo imaging. Subsequently, ultrathin sections of tumor were imaged by using cLSM. Both in vivo and ex vivo imaging results confirmed the tumor-targeted imaging efficiency of QD-Ab probes compared to unconjugated QDs.

Vijayan, V. M., S. J. Shenoy, et al. "Stimulus responsive nanogel with innate near IR fluorescent capability for drug delivery and bioimaging." Colloids Surf B Biointerfaces. 2016 Oct 1;146:84-96. doi: 10.1016/j.colsurfb.2016.05.059. Epub 2016 May 20.

A brighter, non toxic and biocompatible optical imaging agent is one of the major quests of biomedical research. Here in, we report a photoluminescent comacromer [PEG-poly(propylene fumarate)-citric acid-glycine] and novel stimulus (pH) responsive nanogel endowed with excitation wavelength dependent fluorescence (EDF) for combined drug delivery and bioimaging applications. The comacromer when excited at different wavelengths in visible region from 400nm to 640nm exhibits fluorescent emissions from 510nm to 718nm in aqueous condition. It has high Stokes shift (120nm), fluorescent lifetime (7 nanoseconds) and quantum yield (50%). The nanogel, C-PLM-NG, prepared with this photoluminescent comacromer and N,N-dimethyl amino ethylmethacrylate (DMEMA) has spherical morphology with particle size around 100nm and 180nm at pH 7.4 (physiological) and 5.5 (intracellular acidic condition of cancer cells) respectively. The studies on fluorescence characteristics of C-PLM NG in aqueous condition reveal large red-shift with emissions from 523nm to 700nm for excitations from 460nm to 600nm ascertaining the EDF characteristics. Imaging the near IR emission with excitation at 535nm was accomplished using cut-off filters. The nanogel undergoes pH responsive swelling and releases around 50% doxorubicin (DOX) at pH 5.5 in comparison with 15% observed at pH 7.4. The studies on in vitro cytotoxicity with MTT assay and hemolysis revealed that the present nanogel is non-toxic. The DOX-loaded C-PLM-NG encapsulated in Hela cells induces lysis of cancer cells. The inherent EDF characteristics associated with C-PLM NG enable cellular imaging of Hela cells. The studies on biodistribution and clearance mechanism of C-PLM-NG from the body of mice reveal bioimaging capability and safety of the present nanogel. This is the first report on a polymeric nanogel with innate near IR emissions for bioimaging applications.

Wang, F. X., M. H. Chen, et al. "Ester-Modified Cyclometalated Iridium(III) Complexes as Mitochondria-Targeting Anticancer Agents." Sci Rep. 2016 Dec 13;6:38954. doi: 10.1038/srep38954.

Organometallic iridium complexes are potent anticancer candidates which act through different mechanisms from cisplatin-based chemotherapy regimens. Here, ten phosphorescent cyclometalated iridium(III) complexes containing 2,2'-bipyridine-4,4'-dicarboxylic acid and its diester derivatives as ligands are designed and synthesized. The modification by ester group, which can be hydrolysed by esterase, facilitates the adjustment of drug-like properties. The quantum yields and emission lifetimes are influenced by variation of the ester substituents on the Ir(III) complexes. The cytotoxicity of these Ir(III) complexes is correlated with the length of their ester groups. Among them, 4a and 4b are found to be highly active against a panel of cancer cells screened, including cisplatin-resistant cancer cells. Mechanism studies in vitro indicate that they undergo hydrolysis of ester bonds, accumulate in mitochondria, and induce a series of cell-death related events mediated by mitochondria. Furthermore, 4a and 4b can induce pro-death autophagy and apoptosis simultaneously. Our study indicates that ester modification is a simple and feasible strategy to enhance the anticancer potency of Ir(III) complexes.

Wang, G., Y. Guo, et al. "Mitochondria-Mediated Protein Regulation Mechanism of Polymorphs-Dependent Inhibition of Nanoselenium on Cancer Cells." Sci Rep. 2016 Aug 12;6:31427. doi: 10.1038/srep31427.

The present study was (i) to prepare two types of selenium nanoparticles, namely an amorphous form of selenium quantum dots (A-SeQDs) and a crystalline form of selenium quantum dots (C-SeQDs); and (ii) to investigate the nano-bio interactions of A-SeQDs and C-SeQDs in MCF-7, HepG2, HeLa, NIH/3T3, L929 cells and BRL-3A cells. It was found that A-SeQDs could induce the mitochondria-mediated apoptosis, necrosis and death of cells, while C-SeQDs had much weaker effects. This polymorphs-dependent anti-proliferative activity of nano-selenium was scarcely reported. Further investigation demonstrated that A-SeQDs could differentially regulate 61 proteins and several pathways related to stress response, protein synthesis, cell migration and cell cycle, including "p38 MAPK Signaling", "p53 Signaling", "14-3-3-mediated Signaling", "p70S6K Signaling" and "Protein Ubiquitination Pathway". This was the first report to demonstrate the involvement of protein synthesis and post-translational modification pathways in the anti-proliferative activity associated with NMs. Compared with previously fragmentary studies, this study use a nanomics approach combining bioinformatics and proteomics to systematically

investigate the nano-bio interactions of selenium nanoparticles in cancer cells.

Wang, H., X. Wang, et al. "A SPR biosensor based on signal amplification using antibody-QD conjugates for quantitative determination of multiple tumor markers." Sci Rep. 2016 Sep 12;6:33140. doi: 10.1038/srep33140.

The detection of tumor markers is very important in early cancer diagnosis; however, tumor markers are usually present at very low concentrations, especially in the early stages of tumor development. Surface plasmon resonance (SPR) is widely used to detect biomolecular interactions; it has inherent advantages of being high-throughput, real-time, and label-free technique. However, its sensitivity needs essential improvement for practical applications. In this study, we developed a signal amplification strategy using antibody-quantum dot (QD) conjugates for the sensitive and quantitative detection of alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and cytokeratin fragment 21-1 (CYFRA 21-1) in clinical samples. The use of a dual signal amplification strategy using AuNP-antibody and antibody-QD conjugates increased the signal amplification by 50-folds. The constructed SPR biosensor showed a detection limit as low as 0.1 ng/mL for AFP, CEA, and CYFRA 21-1. Moreover, the results obtained using this SPR biosensor were consistent with those obtained using the electrochemiluminescence method. Thus, the constructed SPR biosensor provides a highly sensitive and specific approach for the detection of tumor markers. This SPR biosensor can be expected to be readily applied for the detection of other tumor markers and can offer a potentially powerful solution for tumor screening.

Wang, J., F. Kato, et al. "Automatic Estimation of Volumetric Breast Density Using Artificial Neural Network-Based Calibration of Full-Field Digital Mammography: Feasibility on Japanese Women With and Without Breast Cancer." J Digit Imaging. 2016 Nov 10.

Breast cancer is the most common invasive cancer among women and its incidence is increasing. Risk assessment is valuable and recent methods are incorporating novel biomarkers such as mammographic density. Artificial neural networks (ANN) are adaptive algorithms capable of performing pattern-to-pattern learning and are well suited for medical applications. They are potentially useful for calibrating full-field digital mammography (FFDM) for quantitative analysis. This study uses ANN modeling to estimate volumetric breast density (VBD) from FFDM on Japanese women with and without breast cancer. ANN calibration of VBD was performed using phantom data for one FFDM system. Mammograms of 46 Japanese women diagnosed with invasive carcinoma and 53 with negative findings were analyzed using ANN models learned. ANN-estimated VBD was validated against phantom data, compared intra-patient, with qualitative composition scoring, with MRI VBD, and inter-patient with classical risk factors of breast cancer as well as cancer status. Phantom validations reached an R 2 of 0.993. Intra-patient validations ranged from R 2 of 0.789 with VBD to 0.908 with breast volume. ANN VBD agreed well with BI-RADS scoring and MRI VBD with R 2 ranging from 0.665 with VBD to 0.852 with breast volume. VBD was significantly higher in women with cancer. Associations with age, BMI, menopause, and cancer status previously reported were also confirmed. ANN modeling appears to produce reasonable measures of mammographic density validated with phantoms, with existing measures of breast density, and with classical biomarkers of breast cancer. FFDM VBD is significantly higher in Japanese women with cancer.

Wang, J., X. Tan, et al. "MoS2 Quantum Dot@Polyaniline Inorganic-Organic Nanohybrids for in Vivo Dual-Modal Imaging Guided Synergistic Photothermal/Radiation Therapy." ACS Appl Mater Interfaces. 2016 Sep 21;8(37):24331-8. doi: 10.1021/acsami.6b08391. Epub 2016 Sep 7.

In this study, we introduce a versatile nanomaterial based on MoS2 quantum dot@polyaniline (MoS2@PANI) inorganic-organic nanohybrids, which exhibit good potential to not only enhance photoaccoustic (PA) imaging/X-ray computed tomography (CT) signal but also perform efficient radiotherapy (RT)/photothermal therapy (PTT) of cancer. Upon the intravenous injection of MoS2@PANI hybrid nanoparticles, the in vivo tumor could be precisely positioned and thoroughly eliminated under the PA/CT image-guided combination therapy of PTT/RT. This versatile nanohybrid could show good potential to facilitate simultaneously dual-modal imaging and synergetic PTT/RT to realize better anticancer efficiency.

Wang, J., Y. Zhang, et al. "Enhanced fluorescence of tetrasulfonated zinc phthalocyanine by graphene quantum dots and its application in molecular sensing/imaging." Luminescence. 2016 Oct 10. doi: 10.1002/bio.3223.

When excited at 435 nm, tetra-sulfonate zinc phthalocyanine (ZnPcS4) emitted dual fluorescence at 495 and 702 nm. The abnormal fluorescence at 495 nm was experimentally studied and analyzed in detail for the first time. The abnormal fluorescence at 495 nm was deduced to originate from triplet-triplet (T-T)

energy transfer of excited phthalocyanine (3 *ZnPcS4). Furthermore, graphene quantum dots (GQDs) enhanced the 495 nm fluorescence quantum yield (Q) of ZnPcS4 . The fluorescence properties of ZnPcS4 -GQDs conjugate were retained in a cellular environment. Based on the fluorescence of ZnPcS4 -GQDs conjugate, we designed and prepared an Apt29/thrombin/Apt15 sandwich thrombin sensor with high specificity and affinity. This cost-saving, simple operational sensing strategy can be extended to use in sensing/imaging of other biomolecules.

Wei, N., Z. Zhou, et al. "A novel diarylheptanoid-bearing sesquiterpene moiety from the rhizomes of Alpinia officinarum." Nat Prod Res. 2016 Oct;30(20):2344-9. doi: 10.1080/14786419.2016.1185716. Epub 2016 May 25.

A new diarylheptanoid analogue-bearing sesquiterpene moiety, named Alpinisin A, was isolated from the rhizomes of Alpinia officinarum Hance. The new structure was determined by various spectroscopic techniques (1)H-nuclear magnetic resonance ((1)H NMR), (13)C-attached proton test ((13)C-APT), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond correlation (HMBC), (1)H-(1)H correlation spectroscopy ((1)H-(1)HCOSY), nuclear overhauser effect spectroscopy (NOESY) and high resolution electrospray ionization mass spectrometry (HR-ESI-MS). The compound was tested for cytotoxic activity in vitro against human tumour cell lines (gastric carcinoma cell -7901 (SGC-7901), Michigan Cancer Foundation-7 (MCF-7) and Caski), which showed significant inhibitory effects with IC50 levels of 11.42, 15.14 and 14.78 muM, respectively. The novel chemical structure characterised with a diarylheptanoid linked to a chain-like sesquiterpenoid should be highlighted.

Wu, L. P., M. Ficker, et al. "Poly-(amidoamine) dendrimers with a precisely core positioned sulforhodamine B molecule for comparative biological tracing and profiling." J Control Release. 2016 Dec 29;246:88-97. doi: 10.1016/j.jconrel.2016.12.016.

We report on a simple robust procedure for synthesis of generation-4 poly-(amidoamine) (PAMAM) dendrimers with a precisely core positioned single sulforhodamine B molecule. The labelled dendrimers exhibited high fluorescent quantum yields where the absorbance and fluorescence spectrum of the fluorophore was not affected by pH and temperature. Since the stoichiometry of the fluorophore to the dendrimer is 1:1, we were able to directly compare uptake kinetics, the mode of uptake, trafficking and safety of dendrimers of different end-terminal functionality (carboxylated vs. pyrrolidonated) by two phenotypically different human endothelial cell types (the human brain capillary endothelial cell line hCMEC/D3 and human umbilical vein endothelial cells), and without interference of the fluorophore in uptake processes. The results demonstrate comparable uptake kinetics and a predominantly clathrin-mediated endocytotic mechanism, irrespective of dendrimer end-terminal functionality, where the majority of dendrimers are directed to the endo-lysosomal compartments in both cell types. A minor fraction of dendrimers, however, localize to endoplasmic reticulum and the Golgi apparatus, presumably through the recycling endosomes. In contrast to amino-terminated PAMAM dendrimers, we confirm safety of carboxylic acid- and pyrrolidone-terminated PAMAM dendrimers through determination of cell membrane integrity and comprehensive respiratory profiling (measurements of mitochondrial oxidative phosphorylation and determination of its coupling efficiency). Our dendrimer core-labelling approach could provide a new conceptual basis for improved understanding of dendrimer performance within biological settings.

Wu, S., L. Liu, et al. "Multiplexed detection of lung cancer biomarkers based on quantum dots and microbeads." Talanta. 2016 Aug 15;156-157:48-54. doi: 10.1016/j.talanta.2016.05.005. Epub 2016 May 2.

We have developed a multiplexed fluoroimmunoassay of three lung cancer biomarkers based on multicolor quantum dots (QDs) as detection elements and micro-magnetic beads as immune carriers. QDs have the ability to simplify multiplexed analysis. In our method, the fluorescent signals derived from three cross-talk-free QD conjugated probes with emission maxima at 525, 585 and 625nm could be analyzed to determine the concentrations of the target proteins. With this system, fragments of cytokeratin 19 (CYRFA 21-1), carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE), were simultaneously detected in a single sample with a low detection limit down to the 1.0ng/mL level (364pg/mL for CYRFA 21-1, 38pg/mL for CEA, 370pg/mL for NSE in a single detection). Additional advantages of the presented method include ease of operation, low cost, and a very low sample volume (20microL).

Xi, J., C. Xie, et al. "Pd Nanoparticles Decorated N-Doped Graphene Quantum Dots@N-Doped Carbon Hollow Nanospheres with High Electrochemical Sensing Performance in Cancer Detection." ACS Appl Mater Interfaces. 2016 Aug 31;8(34):22563-73. doi: 10.1021/acsami.6b05561. Epub 2016 Aug 17.

The development of carbon based hollow-structured nanospheres (HNSs) materials has stimulated growing interest due to their controllable structure, high specific surface area, large void space,

enhanced mass transport, and good biocompatibility. The incorporation of functional nanomaterials into their core and/or shell opens new horizons in designing functionalized HNSs for a wider spectrum of promising applications. In this work, we report a new type of functionalized HNSs based on Pd nanoparticles (NPs) decorated double shell structured N-doped graphene quantum dots (NGQDs)@N-doped carbon (NC) HNSs, with ultrafine Pd NPs and "nanozyme" NGQDs as dual signal-amplifying nanoprobes, and explore their promising application as a highly efficient electrocatalyst in electrochemical sensing of a newly emerging biomarker, i.e., hydrogen peroxide (H2O2), for cancer detection. Due to the synergistic effect of the robust and conductive HNS supports and catalytically active Pd NPs and NGQD in facilitating electron transfer, the NGQD@NC@Pd HNS hybrid material exhibits high electrocatalytic activity toward the direct reduction of H2O2 and can promote the electrochemical reduction reaction of H2O2 at a favorable potential of 0 V, which effectively restrains the redox of most electroactive species in physiological samples and eliminates interference signals. The resultant electrochemical H2O2 biosensor based hybrid HNSs materials demonstrates attractive performance, including low detection limit down to nanomole level, short response time within 2 s, as well as high sensitivity, reproducibility, selectivity, and stability, and have been used in real-time tracking of trace amounts of H2O2 secreted from different living cancer cells in a normal state and treated with chemotherapy and radiotherapy.

Xiong, R., F. Joris, et al. "Cytosolic Delivery of Nanolabels Prevents Their Asymmetric Inheritance and Enables Extended Quantitative in Vivo Cell Imaging." Nano Lett. 2016 Oct 3.

Long-term in vivo imaging of cells is crucial for the understanding of cellular fate in biological processes in cancer research, immunology, or in cell-based therapies such as beta cell transplantation in type I diabetes or stem cell therapy. Traditionally, cell labeling with the desired contrast agent occurs ex vivo via spontaneous endocytosis, which is a variable and slow process that requires optimization for each particular label-cell type combination. Following endocytic uptake, the contrast agents mostly remain entrapped in the endolysosomal compartment, which leads to signal instability, cytotoxicity, and asymmetric inheritance of the labels upon cell division. Here, we demonstrate that these disadvantages can be circumvented by delivering contrast agents directly into the cytoplasm via vapor nanobubble photoporation. Compared to classic endocytic uptake, photoporation resulted in 50 and 3 times higher loading of fluorescent dextrans and quantum dots, respectively, with improved signal stability and reduced cytotoxicity. Most interestingly, cytosolic delivery by photoporation prevented asymmetric inheritance of labels by daughter cells over subsequent cell generations. Instead, unequal inheritance of endocytosed labels resulted in a dramatic increase in polydispersity of the amount of labels per cell with each cell division, hindering accurate quantification of cell numbers in vivo over time. The combined benefits of cell labeling by photoporation resulted in a marked improvement in long-term cell visibility in vivo where an insulin producing cell line (INS-1E cell line) labeled with fluorescent dextrans could be tracked for up to two months in Swiss nude mice compared to 2 weeks for cells labeled by endocytosis.

Xu, X., F. Gao, et al. "Selective recognition of cis-trans-isomers of platinum drugs and the detection of triplex DNA based on fluorescence reversible model of quantum dots." J Pharm Biomed Anal. 2017 Feb 5;134:94-99. doi: 10.1016/j.jpba.2016.11.033. Epub 2016 Nov 19.

The identification of spatial structures of drugs and the researches on their interaction mechanism with DNA are always attractive to the researchers. However, their realization is lack of simple and fast method. This paper reports the establishment of multiple-functional detection platform based on the "turn off-on" model of ZnCdSe quantum dots. In this system, ZnCdSe quantum dots work as the fluorescent probe, platinum anti-cancer drugs as the quencher and triplex DNA as the trapping agent. The seemingly similar cisplatin and transplatin exhibited different fluorescent recovery behaviors due to their difference in structure, and thus realized the selective detection of cisplatin and transplatin with the reaction time set at 10min as well as the quantitation of cisplatin over the range of 2.5x10-8-100x10-8M. Based on this, the interactions between platinum anti-cancer drugs and ctDNA as well as polymorphic DNA were further studied, and realized the recognition of triplex DNA. The multiple-functional detection platform integrates the functions of the filtration of high-efficient platinum anti-cancer drugs, the researches on interaction mechanism of drugs, and the recognition of polymorphic DNA, meaningful to the future treatment of viral and cancers based on antisense gene strategy.

Yaghini, E., H. D. Turner, et al. "In vivo biodistribution studies and ex vivo lymph node imaging using heavy metal-free quantum dots." Biomaterials. 2016 Oct;104:182-91. doi: 10.1016/j.biomaterials.2016.07.014. Epub 2016 Jul 12.

Quantum dots (QDs) are attractive photoluminescence probes for biomedical imaging due

to their unique photophysical properties. However, the potential toxicity of QDs has remained a major obstacle to their clinical use because they commonly incorporate the toxic heavy metal cadmium within the core of the QDs. In this work, we have evaluated a novel type of heavy metal-free/cadmium-free and biocompatible QD nanoparticles (bio CFQD((R)) nanoparticles) with a good photoluminescence quantum yield. Sentinel lymph node mapping is an increasingly important treatment option in the management of breast cancer. We have demonstrated their potential for lymph node mapping by ex vivo imaging of regional lymph nodes after subcutaneous injection in the paw of rats. Using photoluminescence imaging and chemical extraction measurements based on elemental analysis by inductively coupled plasma mass spectroscopy, the quantum dots are shown to accumulate quickly and selectively in the axillary and thoracic regional lymph nodes. In addition, lifetime imaging microscopy of the QD photoluminescence indicates minimal perturbation to their photoluminescence properties in biological systems.

Yan, X., K. Wang, et al. "CdSe/ZnS Quantum Dot-Labeled Lateral Flow Strips for Rapid and Quantitative Detection of Gastric Cancer Carbohydrate Antigen 72-4." Nanoscale Res Lett. 2016 Dec;11(1):138. doi: 10.1186/s11671-016-1355-3. Epub 2016 Mar 11.

Carbohydrate antigen 72-4 (CA72-4) is an important biomarker associated closely with diagnosis and prognosis of early gastric cancer. How to realize quick, sensitive, specific, and quantitative detection of CA72-4 in clinical specimens has become a great requirement. Herein, we reported a CdSe/ZnS quantum dot-labeled lateral flow test strip combined with a charge-coupled device (CCD)-based reader was developed for rapid, sensitive, and quantitative detection of CA72-4. Two mouse monoclonal antibodies (mAbs) against CA72-4 were employed. One of them was coated as a test line, while another mAb was labeled with quantum dots and coated onto conjugate pad. The goat anti-mouse IgG was immobilized as a control line. After sample was added, a sandwich structure was formed with CA72-4 and these two mAbs. The fluorescent signal from quantum dots (QD)-labeled mAb in sandwich structure was related to the amount of detected CA72-4. A CCD-based reader was used to realize quantitative detection of CA72-4. Results showed that developed QD-labeled lateral flow strips to detect CA72-4 biomarker with the sensitivity of 2 IU/mL and 10 min detection time. One hundred sera samples from clinical patients with gastric cancer and healthy people were used to confirm specificity of this strip method; results showed that established strip method own 100 % reproducibility and 100 % specificity compared with Roche electrochemiluminescence assay results. In conclusion, CdSe/ZnS quantum dot-labeled lateral flow strips for detection of CA72-4 could realize rapid, sensitive, and specific detection of clinical samples and could own great potential in clinical translation in near future.

Yan, Z. Y., L. L. Wang, et al. "Construction of photodynamic-effect immunofluorescence probes by a complex of quantum dots, immunoglobulin G and chlorin e6 and their application in HepG2 cell killing." Luminescence. 2016 Sep;31(6):1174-81. doi: 10.1002/bio.3054. Epub 2015 Nov 10.

In this study, tri-functional immunofluorescent probes (Ce6-IgG-QDs) based on covalent combinations of quantum dots (QDs), immunoglobulin G (IgG) and chlorin e6 (Ce6) were developed and their photodynamic ability to induce the death of cancer cells was demonstrated. Strategically, one type of second-generation photosensitizer, Ce6, was first coupled with anti-IgG antibody using the EDC/NHS cross-linking method to construct the photosensitive immunoconjugate Ce6-IgG. Then, a complex of Ce6-IgG-QDs immunofluorescent probes was obtained in succession by covalently coupling Ce6-IgG to water soluble CdTe QDs. The as-manufactured Ce6-IgG-QDs maintained the bio-activities of both the antigen-antibody-based tumour targeting effects of IgG and the photodynamic-related anticancer activities of Ce6. By way of polyclonal antibody interaction with rabbit anti-human epidermal growth factor receptor (anti-EGFR antibody, N-terminus), Ce6-IgG-QDs were labelled indirectly onto the surface of human hepatocarcinoma (HepG2) cells in cell recognition and killing experiments. The results indicated that the Ce6-IgG-QDs probes have excellent tumour cell selectivity and higher photosensitivity in photodynamic therapy (PDT) compared with Ce6 alone, due to their antibody-based specific recognition and location of HepG2 cells and the photodynamic effects of Ce6 killed cells based on efficient fluorescence resonance energy transfer between QDs and Ce6. Copyright (c) 2015 John Wiley & Sons, Ltd.

Yang, C. Y., J. G. Phillips, et al. "Buried Hydrogen Bond Interactions Contribute to the High Potency of Complement Factor D Inhibitors." ACS Med Chem Lett. 2016 Sep 13;7(12):1092-1096. eCollection 2016 Dec 8.

Aberrant activation of the complement system is associated with diseases, including paroxysmal nocturnal hemoglobinuria and age-related macular degeneration. Complement factor D is the rate-limiting enzyme for activating the alternative pathway in the complement system. Recent development led to a class of potent amide containing

pyrrolidine derived factor D inhibitors. Here, we used biochemical enzymatic and biolayer interferometry assays to demonstrate that the amide group improves the inhibitor potency by more than 80-fold. Our crystal structures revealed buried hydrogen bond interactions are important. Molecular orbital analysis from quantum chemistry calculations dissects the chemical groups participating in these interactions. Free energy calculation supports the differential contributions of the amide group to the binding affinities of these inhibitors. Cell-based hemolysis assay confirmed these compounds inhibit factor D mediated complement activation via the alternative pathway. Our study highlights the important interactions contributing to the high potency of factor D inhibitors reported recently.

Yang, H. Y., Y. Fu, et al. "Multifunctional Polymer Ligand Interface CdZnSeS/ZnS Quantum Dot/Cy3-Labeled Protein Pairs as Sensitive FRET Sensors." ACS Appl Mater Interfaces. 2016 Dec 28;8(51):35021-35032. doi: 10.1021/acsami.6b12877. Epub 2016 Dec 16.

High-quality CdZnSeS/ZnS alloyed core/thick-shell quantum dots (QDs) as energy donors were first exploited in Forster resonance energy transfer (FRET) applications. A highly efficient ligand-exchange method was used to prepare low toxicity, high quantum yield, stabile, and biocompatible CdZnSeS/ZnS QDs densely capped with multifunctional polymer ligands containing dihydrolipoic acid (DHLA). The resulting QDs can be applied to construct QDs-based Forster resonance energy transfer (FRET) systems by their high affinity interaction with dye cyanine 3 (Cy3)-labeled human serum albumin (HSA). This QD-based FRET protein complex can serve as a sensitive sensor for probing the interaction of clofazimine with proteins using fluorescence spectroscopic techniques. The ability of FRET imaging both in vitro and in vivo not only reveals that the current FRET system can remain intact for 2 h but also confirms the potential of the FRET system to act as a nanocarrier for intracellular protein delivery or to serve as an imaging probe for cancer diagnosis.

Yang, M. Y., J. Hong, et al. "Bio-compatibility and cytotoxicity studies of water-soluble CuInS2-ZnS-AFP fluorescence probe in liver cancer cells." Hepatobiliary Pancreat Dis Int. 2016 Aug;15(4):406-11.

BACKGROUND: The oncogenesis of hepatocellular carcinoma (HCC) is not clear. The current methods of the pertinent studies are not precise and sensitive. The present study was to use liver cancer cell line to explore the bio-compatibility and cytotoxicity of ternary quantum dots (QDs) probe and to evaluate the possible application of QDs in HCC. METHODS: CuInS2-ZnS-AFP fluorescence probe was designed and synthesized to label the liver cancer cell HepG2. The cytotoxicity of CuInS2-ZnS-AFP probe was evaluated by MTT experiments and flow cytometry. RESULTS: The labeling experiments indicated that CuInS2-ZnS QDs conjugated with AFP antibody could enter HepG2 cells effectively and emit intensive yellow fluorescence by ultraviolet excitation without changing cellular morphology. Toxicity tests suggested that the cytotoxicity of CuInS2-ZnS-AFP probe was significantly lower than that of CdTe-ZnS-AFP probe (t test, F=0.8, T=-69.326, P<0.001). For CuInS2-ZnS-AFP probe, time-effect relationship was presented in intermediate concentration (>20%) groups (P<0.05) and dose-effect relationship was presented in almost all of the groups (P<0.05). CONCLUSION: CuInS2-ZnS-AFP QDs probe had better bio-compatibility and lower cytotoxicity compared with CdTe-ZnS-AFP probe, and could be used for imaging the living cells in vitro.

Yang, X., Y. Wang, et al. "One-step synthesis of photoluminescent carbon dots with excitation-independent emission for selective bioimaging and gene delivery." J Colloid Interface Sci. 2016 Dec 24;492:1-7. doi: 10.1016/j.jcis.2016.12.057.

Photoluminescent carbon dots (C-dots), as new members of the quantum sized carbon analogues have attracted significant attention due to their unique size, less toxicity, good compatibility and relatively easy surface modification. In this work, we report a simple, low-cost and one-step hydrothermal carbonization approach to synthesize the positively charged C-dots using PEI and FA. From the photoluminescence (PL) measurements, the as-prepared C-dots exhibit good stability and intense PL with the high quantum yield (QY) at Ca. 42%. Significantly, The as-prepared C-dots integrate the advantages of C-dots and PEI: the presence of C-dots can effectively decrease the cytotoxicity of PEI, the C-dots can be applied in biological system for selective imaging of folate receptor (FR)-positive cancerous cells from normal cells, while the cationic PEI with positive charges can make them link to plasmid DNA and efficiently transfect the therapeutic plasmid into cells. Therefore, the as-prepared with the facile synthesis method can be a promising photoluminescent probe for cancer diagnosis and gene therapy.

Yeh, C. Y., J. K. Hsiao, et al. "Peptide-conjugated nanoparticles for targeted imaging and therapy of prostate cancer." Biomaterials. 2016 Aug;99:1-15. doi: 10.1016/j.biomaterials.2016.05.015. Epub 2016 May 12.

While there has been extensive development of anti-cancer drugs for treatment of prostate cancer, the therapeutic efficacy of such drugs remains inadequate in many cases. Here, we performed in vitro biopanning of the PC3 human prostate carcinoma cell line to select prostate cancer-specific peptides by phage display. We successfully identified specific peptides targeting prostate cancer cells, and their specificity was confirmed by cellular ELISA and flow cytometry. Moreover, we found that the phage clones also recognize other prostate cancer cell lines and surgical specimens from prostate cancer patients. The tumor targeting ability of these phages was validated in a xenograft model, in which high accumulation of targeting phage was observed. To investigate whether selected peptides are able to target tumors and enhance drug delivery into cancer cells, we synthesized peptide-PEGylated lipids and post-inserted them into preformed liposomal doxorubicin and vinorelbine. The results of our cellular uptake and MTT assays indicate that peptide-conjugated liposomes exhibit enhanced drug intracellular delivery and cytotoxicity. The conjugation of targeting peptide to imaging agents, such as quantum dots (QDs) and superparamagnetic iron oxide nanoparticles (SPIONs), results in more precise delivery of these agents to tumor sites. Furthermore, administration of liposomal doxorubicin and vinorelbine conjugated with targeting peptides was found to markedly increase the inhibition of human prostate tumor growth in mouse xenograft and orthotopic models. These results indicate that targeting peptide, SP204, has significant potential for targeted therapy and molecular imaging in prostate cancer.

Yoo, B., K. Son, et al. "Half-Fan-Based Intensity-Weighted Region-of-Interest Imaging for Low-Dose Cone-Beam CT in Image-Guided Radiation Therapy." Healthc Inform Res. 2016 Oct;22(4):316-325. Epub 2016 Oct 31.

OBJECTIVES: With the increased use of computed tomography (CT) in clinics, dose reduction is the most important feature people seek when considering new CT techniques or applications. We developed an intensity-weighted region-of-interest (IWROI) imaging method in an exact half-fan geometry to reduce the imaging radiation dose to patients in cone-beam CT (CBCT) for image-guided radiation therapy (IGRT). While dose reduction is highly desirable, preserving the high-quality images of the ROI is also important for target localization in IGRT. METHODS: An intensity-weighting (IW) filter made of copper was mounted in place of a bowtie filter on the X-ray tube unit of an on-board imager (OBI) system such that the filter can substantially reduce radiation exposure to the outer ROI. In addition to mounting the IW filter, the lead-blade collimation of the OBI was adjusted to produce an exact half-fan scanning geometry for a further reduction of the radiation dose. The chord-based rebinned backprojection-filtration (BPF) algorithm in circular CBCT was implemented for image reconstruction, and a humanoid pelvis phantom was used for the IWROI imaging experiment. RESULTS: The IWROI image of the phantom was successfully reconstructed after beam-quality correction, and it was registered to the reference image within an acceptable level of tolerance. Dosimetric measurements revealed that the dose is reduced by approximately 61% in the inner ROI and by 73% in the outer ROI compared to the conventional bowtie filter-based half-fan scan. CONCLUSIONS: The IWROI method substantially reduces the imaging radiation dose and provides reconstructed images with an acceptable level of quality for patient setup and target localization. The proposed half-fan-based IWROI imaging technique can add a valuable option to CBCT in IGRT applications.

Yu, H. W., J. H. Jiang, et al. "Preparation of quantum dots CdTe decorated graphene composite for sensitive detection of uric acid and dopamine." Anal Biochem. 2017 Feb 15;519:92-99. doi: 10.1016/j.ab.2016.12.001. Epub 2016 Dec 2.

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

Yu, Y., J. Geng, et al. "Bovine Serum Albulmin Protein-Templated Silver Nanocluster (BSA-Ag13): An Effective Singlet Oxygen Generator for Photodynamic Cancer Therapy." Adv Healthc Mater. 2016 Oct;5(19):2528-2535. doi:

10.1002/adhm.201600312. Epub 2016 Jul 14.

This paper reports a novel synthesis approach of bovine serum albumin (BSA) protein-templated ultrasmall (<2 nm) Ag nanocluster (NC) with strong singlet oxygen generation capacity for photodynamic therapy (PDT). An atomically precise BSA-Ag13 NC (i.e., 13 Ag atoms per cluster) is successfully synthesized for the first time by using NaOH-dissolved NaBH4 solution as the controlling reducing agent. The ubiquitous size of BSA-Ag13 NC results in unique behaviors of its photoexcited states as characterized by the ultrafast laser spectroscopy using time-correlated single photon counting and transient absorption techniques. In particular, triply excited states can be largely present in the excited BSA-Ag13 NC and readily sensitized molecular oxygen to produce singlet oxygen (1 O2) with a high quantum efficiency (approximately 1.26 using Rose Bengal as a standard). This value is much higher than its Au analogue (i.e., approximately 0.07 for BSA-Au25 NC) and the commonly available photosensitizers. Due to the good cellular uptake and inherent biocompatibility imparted by the surface protein, BSA-Ag13 NC can be applied as an effective PDT agent in generating 1 O2 to kill cancer cell as demonstrated in this study.

Zane, H. K., J. K. Doh, et al. "Versatile interacting peptide (VIP) tags for labeling proteins with bright chemical reporters." Chembiochem. 2017 Jan 4. doi: 10.1002/cbic.201600627.

Fluorescence microscopy is an essential tool for the biosciences, enabling the direct observation of proteins in their cellular environment. New methods that facilitate attachment of photostable synthetic fluorophores with genetic specificity are needed to advance the frontiers of biological imaging. Here we describe a new set of small, selective, genetically-encoded tags for proteins based on a heterodimeric coiled-coil interaction between two peptides: CoilY and CoilZ. Proteins expressed as a fusion to CoilZ were selectively labeled with the complementary CoilY fluorescent probe peptide. Fluorophore-labeled target proteins were readily detected in cell lysates with high specificity and sensitivity. We found that these versatile interacting peptide (VIP) tags allowed rapid and specific delivery of bright organic dyes or quantum dots to proteins displayed on living cells. Additionally, we validated that either CoilY or CoilZ could serve as the VIP tag, which enabled us to observe two distinct cell-surface protein targets with this one heterodimeric pair.

Zavari-Nematabad, A., M. Alizadeh-Ghodsi, et al. "Development of quantum-dot-encapsulated liposome-based optical nanobiosensor for detection of telomerase activity without target amplification." Anal Bioanal Chem. 2016 Nov 7.

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 = 0.0444 x + 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, B., J. Wang, et al. "Site-specific Biomimetic Precision Chemistry of Bimodal Contrast Agent with Modular Peptides for Tumor-targeted Imaging." Bioconjug Chem. 2017 Jan 13. doi: 10.1021/acs.bioconjchem.6b00712.

Various biomimetic nanoparticles have been fabricated for cancer nanotheranostics with a diverse range of proteins. However, the operating mechanisms of these reactions are still unclear, especially on the interaction between metal ions and protein, the precise binding sites, and the existence format of nanoparticles. Assuming shortening of the amino acids sequence into several, namely short peptides, it would be much easier to investigate the biomimetic reaction mechanism. In this study, a modular peptide, possessing Au3+ ions coordination motifs and Gd3+ ions chelation sequence, is designed and synthesized. This peptide is experimentally found effective in site-

specific biomimetic synthesis of paramagnetic fluorescent gold nanoclusters (pAuNCs) with a quantum yield of 6.8 %, deep red emission at 676 nm, and potent relaxivity. Gel electrophoresis result declares the two imaging motifs in pAuNCs are quite stable. In vivo fluorescence/MR bimodal imaging show significant tumor enhancement by pAuNCs in tumor-bearing mice. In vivo biodistribution and toxicity study reveal pAuNCs can be gradually cleared from body without damage. This study presents modular peptide can incubate multifunctional nanoparticles in a biomimetic fashion, and hopefully provides a strategy for investigation of mechanism on protein-mediated biomimetic synthesis.

Zhang, M., S. Li, et al. "Fluorescent metallacycle-cored polymers via covalent linkage and their use as contrast agents for cell imaging." Proc Natl Acad Sci U S A. 2016 Oct 4;113(40):11100-11105. Epub 2016 Sep 19.

The covalent linkage of supramolecular monomers provides a powerful strategy for constructing dynamic polymeric materials whose properties can be readily tuned either by the selection of monomers or the choice of functional linkers. In this strategy, the stabilities of the supramolecular monomers and the reactions used to link the monomers are crucial because such monomers are normally dynamic and can disassemble during the linking process, leading to mixture of products. Therefore, although noncovalent interactions have been widely introduced into metallacycle structures to prepare metallosupramolecular polymers, metallacycle-cored polymers linked by covalent bonds have been rarely reported. Herein, we used the mild, highly efficient amidation reaction between alkylamine and N-hydroxysuccinimide-activated carboxylic acid to link the pendent amino functional groups of a rhomboidal metallacycle 10 to give metallacycle-cored polymers P1 and P2, which further yielded nanoparticles at low concentration and transformed into network structures as the concentration increased. Moreover, these polymers exhibited enhanced emission and showed better quantum yields than metallacycle 10 in methanol and methanol/water (1/9, vol/vol) due to the aggregation-induced emission properties of a tetraphenylethene-based pyridyl donor, which serves as a precursor for metallacycle 10. The fluorescence properties of these polymers were further used in cell imaging, and they showed a significant enrichment in lung cells after i.v. injection. Considering the anticancer activity of rhomboidal Pt(II) metallacycles, this type of fluorescent metallacycle-cored polymers can have potential applications toward lung cancer treatment.

Zhang, P., Y. Zhuo, et al. "Dual microRNAs-fueled DNA nanogears: A case of regenerated strategy for multiple electrochemiluminescence detection of microRNAs with single luminophore." Anal Chem. 2016 Dec 19.

The determination of multiple biomarkers from cancer cells features a considerable step toward early diagnosis of cancers. However, realizing different biomarkers detection with single electrochemiluminescence (ECL) luminophore and regenerating the sensing platform remain a compelling goal. Herein, dual miRNAs-fueled DNA nanogears were designed for an enzyme-free ECL biosensor construction to perform the multiple sensitive detection of the microRNA (miRNA) biomarkers with single luminophore. The nanogears were assembled on CdS quantum dots (QDs) modified sensing surface. Using miRNA-21 as motive power, Au nanoparticles (AuNPs)-labeled nanogears B could be activated to roll against nanogear A, increasing the distance between AuNPs and CdS QDs. Thus the significant ECL enhancement of CdS QDs was obtained owing to the ECL energy transfer between AuNPs and CdS QDs, simultaneously realizing the detection of miRNA-21. After the incubation of miRNA-155, nanogear B revolved against nanogear A continuously and realized the close-range of AuNPs and CdS QDs, resulting in the quenching of ECL intensity due to the Forster energy transfer and realizing the analysis of miRNA-155. The successive locomotion of the nanogears led to a significant ECL increasing for analysis of miRNA-21 down to 0.16 fM and a remarkable ECL suppression for determination of miRNA-155 down to 0.33 fM. Impressively, the proposed biosensor was able to be regenerated along with the gears roll against each other. In general, this enzyme-free strategy initiates a new thought to realize the multiple ECL detection with single luminophore, paving the way for applications of nanomachines in biosengsing and clinical diagnosis.

Zhao, M. X. and B. J. Zhu "The Research and Applications of Quantum Dots as Nano-Carriers for Targeted Drug Delivery and Cancer Therapy." Nanoscale Res Lett. 2016 Dec;11(1):207. doi: 10.1186/s11671-016-1394-9. Epub 2016 Apr 18.

Quantum dots (QDs), nano-carriers for drugs, can help realize the targeting of drugs, and improve the bioavailability of drugs in biological fields. And, a QD nano-carrier system for drugs has the potential to realize early detection, monitoring, and localized treatments of specific disease sites. In addition, QD nano-carrier systems for drugs can improve stability of drugs, lengthen circulation time in vivo, enhance targeted absorption, and improve the distribution and metabolism process of drugs in organization. So, the

development of QD nano-carriers for drugs has become a hotspot in the fields of nano-drug research in recent years. In this paper, we review the advantages and applications of the QD nano-carriers for drugs in biological fields.

Zhao, Y., T. M. Shaffer, et al. "Near-Infrared Quantum Dot and 89Zr Dual-Labeled Nanoparticles for in Vivo Cerenkov Imaging." Bioconjug Chem. 2017 Jan 12. doi: 10.1021/acs.bioconjchem.6b00687.

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

Zheng, H., X. Li, et al. "Quantum dot-based immunofluorescent imaging and quantitative detection of TOP2A and prognostic value in triple-negative breast cancer." Int J Nanomedicine. 2016 Oct 21;11:5519-5529. eCollection 2016.

BACKGROUND: Topoisomerase 2 alpha (TOP2A) is a key enzyme in DNA replication and a target of various cytotoxic agents including anthracyclines. Previous studies evaluating the predictive and prognostic values of TOP2A in breast cancer are contradictory, likely secondary to the use of both different detection methods and different cutoff thresholds for positive status. Our own studies have previously confirmed the advantages of quantum dot-based nanotechnology for quantitative analysis of biomarkers relative to conventional immunohistochemistry (IHC). This study was designed to 1) assess the expression of TOP2A, 2) investigate the relationship between TOP2A expression and major clinical pathological parameters, and 3) evaluate the prognostic value of TOP2A by quantum dot-based immunofluorescent imaging and quantitative analytical system (QD-IIQAS) in triple-negative breast cancer (TNBC). PATIENTS AND METHODS: TOP2A expression in 145 TNBC specimens was detected using IHC and QD-IIQAS, and a comparative analysis of the two methods was conducted, including an exploration of the relationship between TOP2A expression and major clinical pathological parameters in TNBC. The prognostic value of TOP2A in TNBC was assessed. RESULTS: A similar antigen localization, a high correlation of staining rates (r=0.79), and a high agreement of measurements (kappa=0.763) of TOP2A expression in TNBC were found by QD-IIQAS and conventional IHC (cutoff: 45.0 and 0.45, respectively). TOP2A was significantly higher in larger tumors (P=0.002), higher grade tumors (P=0.005), and lymph node positive patients (P<0.001). The 5-year disease-free survival (5-DFS) of the high and low TOP2A subgroups was significantly different for both QD-IIQAS and IHC (P<0.001, log-rank test for both). TOP2A expression was an independent predictor of survival in TNBC (P=0.001).

Zhou, B., Y. Li, et al. "Near-Infrared Organic Dye-Based Nanoagent for the Photothermal Therapy of Cancer." ACS Appl Mater Interfaces. 2016 Nov 9;8(44):29899-29905. Epub 2016 Oct 26.

Given their easy structural modification and good biocompatibility advantages, near-infrared (NIR) organic dyes with a large molar extinction coefficient, while a superlow fluorescence quantum yield shows considerable potential application in photothermal therapy (PTT). Herein, a new NIR-absorbing asymmetric cyanine dye, namely, RC, is designed and synthesized via the hybrid of rhodamine and hemicyanine derivatives. RC-BSA nanoparticles (NPs) are fabricated by using the bovine serum albumin (BSA) matrix. The NPs exhibit a strong NIR absorption peak at approximately 868 nm and 28.7% photothermal conversion efficiency. Based on these features, RC-BSA NPs exhibit excellent performance in ablating tumor under a 915 nm laser radiation through a PTT mechanism. These NPs show no obvious toxicity to the treated mice. Thus, RC-BSA NPs can used as a new NIR laser-triggered PTT agent in cancer treatment.

Zhu, C. N., G. Chen, et al. "Near-Infrared Fluorescent Ag2 Se-Cetuximab Nanoprobes for Targeted Imaging and Therapy of Cancer." Small. 2017 Jan;13(3). doi: 10.1002/smll.201602309. Epub 2016 Nov 7.

Theranostic nanoprobes integrated with diagnostic imaging and therapy capabilities have shown great potential for highly effective tumor therapy by realizing imaging-guided drug delivery and tumor treatment. Developing novel high-performance

nanoprobes is an important basis for tumor theranostic application. Here, near-infrared (NIR) fluorescent and low-biotoxicity Ag2 Se quantum dots (QDs) have been coupled with cetuximab, a clinical antiepidermal growth factor receptor antibody drug for tumor therapy, via a facile bioconjugation strategy to prepare multifunctional Ag2 Se-cetuximab nanoprobes. Compared with the Ag2 Se QDs alone, the Ag2 Se-cetuximab nanoprobes display faster and more enrichment at the site of orthotopic tongue cancer, and thus present better NIR fluorescence contrast between the tumor and the surrounding regions. At 24 h postinjection, the NIR fluorescence of Ag2 Se-cetuximab nanoprobes at the tumor site is still easily detectable, whereas no fluorescence is observed for the Ag2 Se QDs. Moreover, the Ag2 Se-cetuximab nanoprobes have also significantly inhibited the tumor growth and improved the survival rate of orthotopic tongue cancer-bearing nude mice from 0% to 57.1%. Taken together, the constructed multifunctional Ag2 Se-cetuximab nanoprobes have achieved combined targeted imaging and therapy of orthotopic tongue cancer, which may greatly contribute to the development of nanotheranostics.

Zmejkovski, B. B., N. Pantelic, et al. "In vitro anticancer evaluation of platinum(II/IV) complexes with diisoamyl ester of (S,S)-ethylenediamine-N,N'-di-2-propanoic acid." Anticancer Agents Med Chem. 2016 Dec 7.

Platinum(II) and platinum(IV) complexes [PtCln{(S,S)-(i-Am)2eddip}] (n = 2, 4: 1, 2, respectively; (S,S)-(i-Am)2eddip = O,O'-diisoamyl-(S,S)-ethylenediamine-N,N'-di-2-propanoate) were synthesized and characterized by elemental analysis, IR, 1H and 13C NMR spectroscopy and mass spectrometry. Quantum chemical calculations were used to predict formed isomers of 1 and 2. Furthermore, reduction of 2 with ascorbic acid was followed by time-dependant 13C NMR spectroscopy in order to enable assignation of the formed isomers for complex 1. In vitro cytotoxic activity was determined for 1 and 2 on a panel of five human tumor cell lines derived from cervix adenocarcinoma (HeLa), alveolar basal adenocarcinoma (A549), breast adenocarcinoma (MDA-453), colorectal cancer (LS 174), erythromyeloblastoid leukemia (K562), as well as one non-malignant human lung fibroblast cell line (MRC-5), using MTT assay. Both complexes exhibited high (2 against K562: IC50 = 5.4 microM), more active than cisplatin, to moderate activity (1). Both complexes caused considerable decrease of cell number in K562 cells in G1, S and G2 phases, concordantly increasing subpopulation in sub-G1 fraction. Morphological analysis of K562 cell death induced by platinum(II/IV) complexes indicate apoptosis.

Zou, Y., F. Fang, et al. "Notch 2 signaling contributes to cell growth, anti-apoptosis and metastasis in laryngeal squamous cell carcinoma." Mol Med Rep. 2016 Oct;14(4):3517-24. doi: 10.3892/mmr.2016.5688. Epub 2016 Aug 29.

Notch signaling is important during the development of a variety of human tumors. Depending on the context, Notch signaling can be either oncogenic or antiproliferative, and therefore, its effects in cancer are unpredictable. The aim of the present study was to identify the importance of Notch 2 in the cell growth and metastasis of laryngeal squamous cell carcinoma (LSCC). The current study performed quantum dotsbased immunofluorescence histochemistry to determine expression of Notch 2 in 72 LSCC samples without lymph node metastasis, 23 LSCC samples with lymph node metastasis and 31 samples from vocal cord polyps. It was observed that Notch 2 was upregulated in LSCC tissue compared with normal vocal cord polyps. This upregulation was further enhanced in LSCC tissues with lymph node metastasis compared with LSCC tissues without lymph node metastasis. Following knockdown of NOTCH2 expression in LSCC cells, the in vitro tumorigenicity of Hep2 cells was inhibited, with growth, migration, invasion and proliferation reduced, and apoptosis induced. Additionally, following downregulation of Notch 2 protein expression, the protein expression levels of phosphomitogenactivated protein kinase 1 (pERK), vmyc avian myelocytomatosis viral oncogene homolog and Bcell CLL/lymphoma 2 (Bcl2) were also downregulated, whereas, Bcl2associated X protein expression was upregulated. There were no changes detected in the protein expression levels of totalERK, phosphovakt murine thymoma viral oncogene homolog 1 (pAkt) and totalAkt.

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