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15 YEARS OF COMMERCIALIZING MEDICAL DEVICES USING NANOTECHNOLOGY

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There is an acute shortage of organs due to disease, trauma, congenital defects, and most importantly, age related maladies. The synthetic materials used in tissue engineering applications today are typically composed of millimeter or micron sized particles and/or fiber dimensions. Although human cells are on the micron scale, their individual components, e.g. proteins, are composed of nanometer features. By modifying only the nanofeatures on material surfaces without changing surface chemistry, it is possible to increase tissue growth of any human tissue by controlling the endogenous adsorption of adhesive proteins onto the material surface. In addition, our group has shown that these same nanofeatures and nano-modifications can reduce bacterial growth without using antibiotics, which may further accelerate the growth of antibiotic resistant microbes. Inflammation can also be decreased through the use of nanomaterials. Finally, nanomedicine has been shown to stimulate the growth and differentiation of stem cells, which may someday be used to treat incurable disorders, such as neural damage. This strategy also accelerates USA FDA approval and commercialization efforts since new chemistries are not proposed, rather chemistries already approved by the FDA with altered nanoscale features. This invited talk will highlight some of the advancements and emphasize current nanomaterials approved by the USA FDA for human implantation.

THERANOSTIC NANOPARTICLES FOR TREATMENT OF INFLAMMATORY DISEASE AND CANCER

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The traditional "one treatment fits all" paradigm disregards the heterogeneity between patients, and within a particular disease, thus limit the success of common treatments. Moreover, current treatment lacks specificity and therefore most of the drugs induce some adverse effects. Personalized medicine aims to individualize therapeutic interventions, based on the growing knowledge of the human multiple '-oms' (e.g. genome, epigenome, transcriptome, proteome and metabolome), which has led to the discovery of various biomarkers that can be used to detect for example, early stage cancers and predict tumor progression, drug response, and clinical outcome. Nanomedicine, the application of nanotechnology to healthcare, holds great promise for revolutionizing disease management such as drug delivery, molecular imaging, reduced adverse effects and the ability to contain both therapeutic and diagnostic modalities simultaneously termed theranostics. Personalized nanomedicine has the power of combining nanomedicine with clinical and molecular biomarkers ("OMICS" data) achieving improve prognosis and disease management as well as individualized drug selection and dosage profiling to ensure maximal efficacy and safety. In this presentation I will discuss the immense potential of combining the best of these two worlds, nanomedicine and high throughput OMICS technologies to pave the way towards personalized medicine. Examples will be given from the fields of Oncology (Brain tumors, Ovarian Cancer and Blood cancers) and Inflammation (inflammtory bowel diseases)

TARGETING ATHEROSCLEROSIS USING SUPRAMOLECULAR MICELLAR ASSEMBLIES

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Despite the high level of mortality, the cardiovascular field has not benefited to a similar degree as cancer from recent advances in nanomedicine. Applications of medical nanotechnology toward cancer far out-number those to cardiovascular disease by orders of magnitude. Similarly to cancer applications, nanomedicine can bring numerous powerful advantages, including early detection by amplification of small signals; local, as opposed to systemic, delivery of therapeutics; simultaneous delivery of a battery of agents.
Within cardiovascular disease, atherosclerosis is known to be a leading contributor to morbidity and mortality. Current imaging modalities use techniques that focus on the severity of the blockage within arteries. However, the majority of plaques that rupture and cause a clinical event do not correlate with plaque size. Therefore, early detection is needed, and requires detecting molecular markers that characterize vulnerable plaques.
Peptide-based nanomaterials are particularly useful for these applications as the peptide provides a tool to incorporate a biological epitope for specific homing, with inherent biocompatible and biodegradable characteristic. To this end, we have engineered supramolecular, peptide amphiphile micelles (sPAM) that bind to various stages of atherosclerosis and incorporated imaging agents to act as contrast agents for clinically relevant modalities such as magnetic resonance imaging (MRI). Micelles formed from PAs are advantageous because a locally concentrated display of a peptide on the exterior can be used to potentiate specific binding to a disease target of interest, minimizing systemic side effects. Moreover, the nanometer size provides favorable pharmacokinetic properties *in vivo*. And notably, due to the modularity of PAMs and their ability to incorporate multiple components, theranostic micelles can be easily constructed through simple mixing of the various amphiphilic molecules. Such micelles have the potential to be the next generation of nanoparticles with capabilities to bind to specific disease markers of interest, deliver a therapeutic, and monitor the progression and/or regression of the disease in real-time. We present micelles developed for early to late-stage atherosclerosis, and their potential as contrast-enhancing, diagnostic agents *in vivo*.

RATIONAL DESIGN OF THERANOSTIC POLYMERIC NANOCONSTRUCTS FOR BIOMEDICAL APPLICATIONS

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UNLOCKING INTRACELLULAR THERAPEUTIC TARGETS THROUGH NOVEL NANOSTRUCTURED BIOMATERIALS

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Nucleic acid cargoes offer unmatched diversity in gene regulatory potential and therapeutics, and understanding of nucleic acid functionality continues to expand rapidly and dramatically through seminal discoveries including RNA interference approaches and gene editing technologies. In nature, the basis for gene regulation is ultimately encoded by the exquisite specificity with which cells are able to control both the location and accessibility of nucleic acid constructs to govern their activation states. My research program seeks to understand and control gene activation using synthetic constructs through nature-inspired approaches to control and quantify cell binding interactions and stability in polymer and peptide nanocarriers. The basis of our approaches is the design of stimuli-responsive polymers and peptides whose interactions with nucleic acids and cells can be controlled dynamically by specific intracellular or external triggers. We exploit our ability to control nucleic acid binding/release and cellular processing to gain new mechanistic insights over nucleic acid delivery, leading to design advances including histone-inspired DNA targeting, light-responsive gene silencing, and collagen turnover-stimulated gene expression. This talk will highlight two ways we have used nature-inspired peptides to control gene transfer in regenerative medicine.

Our approaches are exemplified by our work in histone-targeted nanocarrier design. Histones have received great interest as potential gene carriers for several decades due to their seminal role in chromatin packaging and gene transfer, yet therapeutic efforts with histones have lacked both a well-controlled materials approach and a deeper knowledge of cellular processing mechanisms. Hence, histone-based carriers have failed to reach clinical efficacy. We have capitalized on newly recognized and highly pivotal roles for histone tails in native gene regulatory control to develop a gene transfer method that utilizes native, histone-based processing pathways *via* incorporation of post-translationally modified (PTM) histone tails within controllably-assembled DNA vehicles (polyplexes). Our efforts proved that polyplexes displaying PTM-modified histone tails promote nuclear accumulation, DNA release, transcription, and enhanced transfection. Moreover, our group has combined detailed nanostructure engineering with sophisticated cellular imaging to identify novel aspects in the cell biology framework regulating polyplex transport to the nucleus.

We have also focused on novel mechanisms to exploit nature's ability to harness extracellular matrix (ECM) proteins such as collagens to sequester and control delivery of bioactive nanostructures. Our specific approaches have capitalized on a class of peptides known as collagen-mimetic peptides, or CMPs, that have been recognized for their unique affinity for native collagen, which can be tailored through alterations in CMP amino acid sequence and molecular weight. CMPs incorporate themselves into the natural collagen triple helical structure via strand invasion, in a reversible process previously that has been used to modify extracted collagen *in vitro* and exclusively target remodeling collagen *in vivo.* In our studies, we employed a proline-rich CMP designed to act not only as an adjustable tether to regulate collagen-polyplex affinity, but also as an adhesive/endocytic ligand for polyplexes. The use of a collagen scaffold afforded our system structural support and innate bioactivity to encourage cellular ingrowth and proliferation, whereas altering the extent of the modification of our vector provided additional tunability to allow tailorable release for prolonged time periods. This CMP-based approach also consistently and fully maintained polyplex activity in the presence of serum for at least a week, whereas most bolus and substrate-mediated gene delivery approaches report rapid reductions within hours or a few days, and the level of transgene expression directly correlated with MMP-concentrations and the extent of collagen remodeling, demonstrating "on demand" release. The ability to tailor release over extended periods via physical attachments, combined with the ability to provide cell-trigger release and collagen-mediated uptake, make this approach very attractive for many applications in regenerative medicine.

CONSTRUCTION OF NANOPARTICLE PLATFORMS FOR EFFECTIVE DRUG AND GENE DELIVERY

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SHAPE-CHANGING NANOMAGNETS: A NEW APPROACH TO IN-VIVO BIOSENSING

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Key Words: Magnetic nanoparticle; nanoprobe; nanosensor; MRI; NMR

The idea that optical color can be determined by size and shape is well known at the nanoscale. Colors of quantum dots and plasmonic nanostructures, for example, can be tuned through particle size and shape. Among others, this has directly enabled many different multi-colored nanoparticle labels that underpin a host of optically-based *in vitro* bioimaging applications, including multiplexed high-throughput bioassays and colorimetric sensing and visualization of biomolecular processes and function. Imaging and sensing in more realistic *in vivo* environments is more challenging, however. Optical probes can be sized or shaped to yield resonances closer to the more optically favorable near-infrared window, but optical penetration, signal intensity, and spatial resolution, still deteriorate rapidly with increasing depth beneath the surface. But what about in the radio-frequency (RF) portion of the spectrum? Are there any analogous nanoparticle structures that can shift the frequency, or equivalently color, of RF signals for which penetration and/or distortion through biological tissue would no longer be a limitation and where imaging and sensing would be naturally immune to any photostability, phototoxicity, and autofluoresence background issues?

This talk will discuss recent progress towards this aim, focusing on new, specially shaped, magnetic nanoparticle structures that are designed to shift the magnetic resonance frequency of surrounding nuclei, effectively using shape to determine the RF frequency, or color, of a resulting nuclear magnetic resonance (NMR) signal. In analogy to optically based nanoparticle probes, different magnetic nanoparticle shapes can yield different resonant frequency shifts, or effectively RF “colors”, enabling multispectral labeling and multiplexed magnetic resonance imaging (MRI). With frequency determined by geometry, magnetic structures that can rapidly, dynamically vary their shape in response to a specific chosen biomarker or physiological condition therefore also function as RF analogues to fluorescent colorimetric sensors, with a potentially similarly broad range of applications[1].

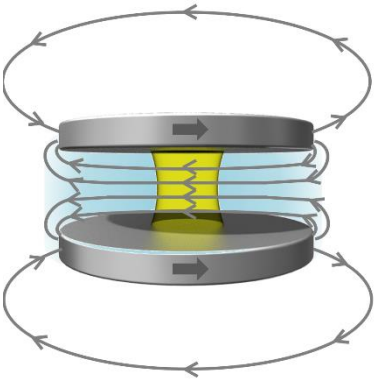

Fig 1. Schematic of shape-shifting magnetic sensor. Expansion of the inner hydrogel post shifts a pair of magnetic disks, changing the magnetic fields that in turn shift the NMR frequency of surrounding water protons.

The new NMR-readable RF sensors respond to their environment through the incorporation of nanoscale, smart (and biocompatible) hydrogel elements, which can be sensitized to a variety of different biomarkers of interest. As the hydrogel changes shape in response to local conditions, changes in the spacing between a pair of attached magnetic elements (see figure), leads to a change in the local magnetic field, which in turn shifts the local NMR water line. In this way, measurements of local physiological conditions are transduced into remotely detectable, quantitative NMR frequency shifts in the surrounding water signal. This talk will discuss in more detail how such structures work, how they can be made, and where they might be applied. As an example, RF-based pH sensing is demonstrated using acid sensitized hydrogel spacer elements, but given the inherent adaptability of the incorporated hydrogel sensing elements it is anticipated that the same measurement platform may be readily converted to measure many other biomarkers.

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TRANSLATIONAL NANOMEDICINE:
TARGETED THERAPEUTIC DELIVERY FOR CANCER AND INFLAMMATORY DISEASES

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Tremendous advances in molecular and personalized medicine also present challenges for translation of innovative experimental approaches into clinically relevant strategies. To overcome some of these challenges, nanotechnology offers interesting solutions for disease prevention, diagnosis, and treatment. For many systemic diseases, overcoming biological barriers and target specific delivery are the key challenges. Additionally, newer generation of molecular therapies, such as gene therapy, oligonucleotides, and RNA interference (RNAi) require robust and highly specific intracellular delivery strategies for effective and clinically meaningful therapeutic outcomes.

In this presentation, I will cover several of our approaches for development of multifunctional engineered nano-systems for targeted therapies in the treatment of cancer, pain, and inflammatory diseases. Specific examples will include: (1) use of combinatorial-designed engineered nano-systems for RNA interference therapy in treatment of tumor multidrug resistance and genetic modulation of macrophage phenotype to promote anti-inflammatory effect in the treatment of autoimmune disorders.

In each of the above examples, we focus on challenging medical problems with innovative solutions that use safe materials and scalable fabrication methods in order to facilitate clinical translation and improve patient outcomes.

ELP-DOXORUBICIN NANOPARTICLES FOR INHIBITING CANCER METASTASIS

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NANOPARTICLES FOR TARGETING CANCER CELLS

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HARNESSING CELL-PARTICLE INTERACTION IN DRUG DELIVERY

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NANOPARTICLES AND BIOLOGICAL CELLS: FROM ATOMISTIC SIMULATIONS TO MEMBRANE DIAGNOSTICS

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Nanomedicine enables unique diagnostic and therapeutic capabilities to tackle problems in clinical medicine. The delivery of drugs, antigens, and imaging agents benefit from using nanotechnology-based carriers. However, from the entry of the therapeutic nanoparticle into the host´s blood circulation, the nanoparticle faces a long journey to its intended destination. During that journey, there are several barriers that need to be overcome. These hurdles are often neglected or disregarded in physiochemical evaluations of the future possibilities of nanotechnology to deliver agents to specific targets.

In this talk we report on our latest results on the interactions of nanoparticles with cellular membranes. The two main questions we want to address are: 1) what are the physicochemical characteristics of nanomaterials that drive their entry into cells? And, 2) can we design nanomaterials in order to achieve selective mode of entry into cells? The results will focus on carbonaceous nanoparticles, including a new class of compounds, carbonaceous quantum dots, which have recently emerged and ignited tremendous research interest. Their favorable characteristics include size- and wavelength-dependent luminescence, resistance to photobleaching, bio-conjugation, and functionalization to produce chiral nanostructures. Carbon-based quantum dots show promise in areas such optoelectronics, catalysis, bioanalysis and drug delivery. Atomistic simulations in conjunction with precise chemical and biophysical experiments are the distinguishing characteristics of this effort. Molecular dynamics simulations will examine the effects of nanoparticles parameters, such as size and chemical composition, on the entry mode of nanoparticles into cells. A conceptual framework is presented that envisions possible routes for the design of nanomaterials for nanomedicine applications.

MARRYING BIOMOLECULES AND NANOPARTICLES FOR DIAGNOSTICS AND NANOMEDICINE

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Key Words: Biomolecules, Nanoparticles, Biofunctionalization, Diagnostics, Nanomedicine

Noble metal nanoparticles (NPs) such as silver and gold NPs, at the size range of 1-100 nm have attracted enormous scientific and technological interest due to their unique optical, electronic and catalytic properties, which are largely determined by their size, shape and crystal structure. Inspired by the natural biomineralization process on using biomolecular templates to form a range of sophisticated inorganic nanostructures, our current research efforts focus on the development of bioinspired metal NPs with tunable physicochemical properties that incorporate the highly specific recognition function of biomolecules for a vast plethora of biomedical applications. Firstly, I will talk about the rational design of peptide and nucleic acid-based biomolecular templates for the biomimetic synthesis of multifunctional metal NPs with different optical properties (i.e., plasmon absorption and light emission) and integrated biofunctionalities for biosensing, imaging, delivery and therapy.[1-7] Recently, we have designed a unique self-assembly DNA templates to form redox-responsive photoluminescent silver nanoclusters (NCs < 2 nm in size) for two-way color change detection of free radicals (red-to-blue) and antioxidants (blue-to-red) in real time. These DNA-templated AgNCs are found to have excellent antimicrobial and toxin inhibition properties towards superbugs. Using bi-functional peptide templates, AuNCs with tunable emission color from visible to near-infrared wavelength have been successfully synthesized for targeted gene delivery and bioimaging applications. We have also employed this bioinspired approach to 'turn' the native protein into bioactive fluorescent sensors for small molecule drug screening and photodynamic therapy. The biocompatibility and adaptability of biomolecules involved in the synthesis enable an efficient control over nanostructures morphology (size and shape) with fine-tuned properties, resulting in low energy use and environmental impact. The second part of my talk will focus on the biofunctionalization strategies of nanometals for the development of ultrasensitive biosensors, to convert 'invisible' biological responses into easily measurable and observable optical outputs.[8-13] By exploiting the plasmonic coupling, fluorescence and/or light scattering properties of the nanometals, we have developed a series of label-free optical nanosensors to detect a wide range of bioanalytes (e.g., vitamins, small molecule drug, etc.) and for studying important biomolecular interactions such as gene transcription, DNA mutation and enzymatic reaction. These bioassays are versatile, efficient and low-cost with high throughput sensing capability, which could culminate into tangible products useful for biomedical research and clinical diagnostics.

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IMPACT OF ENGINEERED NANOPARTICLES IN INITIATING OR MODULATING PATHOLOGY-RELATED INFLAMMATION

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The possibility that nanomaterials could perturb the normal course of an inflammatory response is a key issue when assessing nano-immunosafety. The alteration of the normal progress of an inflammatory response may have pathological consequences, since inflammation is a major defensive mechanism and its efficiency maintains the body's health. We can thus consider as pathology-related inflammation those inflammatory reactions that, instead of eliminating foreign agents, lack down-regulation and cause tissue damage. To assess the ability of nanoparticles to initiate and modulate inflammatory reactions, an *in vitro* model was used that recapitulates all the stages of infection-induced inflammation, from initiation to resolution, based on human primary blood monoytes. A parallel model reproducing pathological chronic inflammation shows that the differences between resolving and persistent inflammation are subtle and evident only upon kinetic analysis of gene expression profiles and production of inflammatory factors. Rigorously endotoxin-free Au and Ag nanoparticles have been assessed for their ability to directly initiate *in vitro* inflammation and for their capacity to modulate the course both physiological resolving inflammation and pathological persistent inflammation. In no case significant effects were observed, with the exception of a transient increase of the inflammatory response in the presence of Ag nanoparticles. An important issue in the regulation of monocyte/macrophage inflammatory functions is the capacity of innate "memory", *i.e.*, the ability of respond differently to a challenge if previously primed with the same or a different agent. How nanoparticles can impact innate memory was assessed by using Au nanoparticles as priming and challenge agent with and without LPS and zymosan. Priming with LPS and zymosan could drastically decrease the response of monocytes (production of TNFα) to a challenge with any stimulus, given 7 days after the first. The presence of Au nanoparticles did not influence such behaviour. Likewise, Au nanoparticles did not directly induce memory, *i.e.*, did not influence the response of monocytes to subsequent stimuli. We conclude that Au and Ag nanoparticles, at the size and concentrations used, are taken up by monocytes without this causing any notable interference with their capacity to mount an adequate defensive responses to microbial challenges, either immediate or after some time from exposure.

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A MECHANISTIC INSIGHT TO NANOMEDICINE-MEDIATED ADVERSE CARDIOPULMONARY REACTIONS

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Pigs are often used as predictive models of nanomedicine-mediated cardiopulmonary distress reactions in humans. Unlike humans, pulmonary intravascular macrophages (PIM) are abundant in pig lungs. Robust phagocytosis of particles by PIM results in immediate release of large quantities of mediators that correlate with periods of peak cardiopulmonary disturbances. This raises questions on relevance of the pig model to human cases. However, there are suggestions of induction of pulmonary macrophages in certain human diseases (e.g., liver and inflammatory lung diseases). It is conceivable that highly responsive patients may have induced PIM, which could increase sensitivity to blood-borne particles, and the potential risk of pulmonary hemodynamic side effects. Accordingly, it would be necessary to search for constitutive or induced PIM in biopsied or autopsied human lungs, map their phenotype in liver and inflammatory lung diseases, and understand the pathologic implication of phagocyte residency in pulmonary capillaries. In this presentation, I will discuss the roles of PIM and the complement system activation on initiation of adverse cardiopulmonary distress on nanomedicine administration as well as simple strategies that could overcome these problems even in the pig model. Alternative animal models will be suggested for investigating the interplay between induced PIM and the complement system that could closely resemble the human cases and applicable for cardiopulmonary risk assessment in relation to biopharmaceuticals/nanomedicine administration.

NOVEL STRATEGY TO DISRUPT THE NUCLEAR PORE BARRIER REVERSIBLY: IMPLICATIONS FOR NANOMEDICINE

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Several thousands of nuclear pore complexes (NPCs) perforate the nuclear envelope of each eukaryotic cell. These elaborate proteinaceous assemblies mediate all nucleocytoplasmic transport highly selectively through a central channel residing within a rigid and well-structured NPC scaffold. The selectivity of the NPCs is the major obstacle for non-viral gene therapy due to the prevention of exogenously applied therapeutic macromolecules from nuclear entry. Selectivity is attributed to highly dynamic and disordered Phenylalanine-Glycine rich proteins within the NPC central channel. The NPC scaffold poses an additional barrier-albeit ignored so far. We designed two distinct strategies to reversibly disrupt the NPC channel and scaffold in a separate fashion. Disruption of either is found to result in a significant increase of the NPC permeability and a combination of the two further intensifies the individual effects. The induced breakdown of the NPC permeability barrier may be exploited for gene therapeutic purposes.

MAGNETIC MATERIALS FOR SMART THERAPY AND DIAGNOSTICS

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Key Words: magnetic nanoparticles, theranostic, core-shell, MRI, drug delivery, superlow-frequency magnetic fields

Magnetic nanoparticles have received significant attention recently and are actively investigated owing to their large potential for a variety of applications. Gold-coated magnetic nanoparticles are a class of nanoparticles that have attracted much attention because of their advantageous characteristics, such as their inertness, non-toxicity, super magneticity, ease of detection in the human body, a magnetic core that is protected against oxidation, their facilitated bio-conjugating ability, catalytic surface, and their potential for a variety of biological applications. Gold-coated nanoparticles have great biocompatibility with the human body with the ability to interact with biomolecules such as polypeptides, DNA, and polysaccharides.

Herein we report a synthetic procedure for the preparation of water-soluble Fe_3O_4, Fe_3O_4@Au core-shell and dumbbell nanoparticles, simple protocol for their synthesis, purification by exclusion chromatography and method for functionalization of gold surface with a number of sulfur-containing ligands (L-cystein, 3-mercaptopropionic acid, 11-mercaptoundecanoic acid, lipoic acid, HS-PEG-COOH, 2-aminoethanethiol, and others). Finally, magnetic nanoparticles were functionalized by immobilization of enzymes, PSMA targeted ligands, fluorescent dyes. These magnetic nanoparticles were characterized by transmission electron microscopy (TEM), FTIR, DLS and UV-Vis spectroscopy.

We describe a distinct effect of non-heating superlow-frequency magnetic fields on the kinetics of chemical reactions catalyzed by the enzymes immobilized on core-shell nanoparticles.The observation is unprecedented and suggests the significance of magneto-mechanochemical effects induced by realignment of MNP magnetic moments in an AC magnetic field rather than traditional heating. Such low frequency and amplitude fields are safe and are not expected to cause any damage to biological tissues.

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SYNTHOPLATE®: A PLATELET-INSPIRED HEMOSTATIC NANOTECHNOLOGY FOR TREATMENT OF BLEEDING COMPLICATIONS

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Platelet transfusions are routinely used in the clinic to treat bleeding complications stemming from trauma, surgery, malignancy-related bone marrow dysfunctions, and congenital or drug-related defects platelet defects. These transfusions primarily use allogeneic platelet concentrates (PCs) that pose issues of limited availability and portability, high risk of bacterial contamination, very short shelf life (~3-5 days), need for antigen matching and several biologic side effects. While robust research is being directed at resolving some of these issues, there is in parallel a significant clinical interest in synthetic platelet substitutes that can render efficient hemostasis by leveraging and amplifying endogenous clotting mechanisms while avoiding the above issues. To this end, we have developed a unique platelet-inspired synthetic hemostat technology called the SynthoPlate® (US Patent 9107845). Since platelets promote primary hemostasis via adhesion to vWF and collagen at the injury site and concomitant aggregation via fibrinogen binding to integrin GPIIb-IIIa on active platelets, we have mimicked and integrated these key hemostatic mechanisms on the SynthoPlate® by heteromultivalent surface-engineering of a liposomal platform with vWF-binding peptides (VBP), collagen-binding peptides (CBP) and fibrinogen-mimetic peptides (FMP). These ~150nm diameter SynthoPlate® vesicles are sterilizable and can be stored as lyophilized powder for long periods of time. We demonstrated, in vitro, that this platelet-mimetic integrative design renders hemostatically relevant functions at levels significantly higher than designs that mimic platelet's adhesion function only or aggregation function only. We further demonstrated in vitro that SynthoPlate®-mediated site-selective amplification of primary hemostatic mechanisms (active platelet recruitment and aggregation) in effect results in site-selective enhancement of secondary hemostatic function (fibrin generation). We also established that SynthoPlate® does not activate and aggregate resting platelets or trigger coagulation mechanisms in plasma, suggesting that this technology will not have systemic pro-thrombotic and coagulatory risks. The hemostatic efficacy of SynthoPlate® was tested in appropriate tail-transection and liver bleeding models in mice, as well as, pilot studies in arterial bleeding model in pigs. In tail-transection bleeding model in normal as well as thrombocytopenic mice, prophylactically administered SynthoPlate® was able to significantly reduce bleeding time by 60-70%. In laparotomy traumatic bleeding model in mice, prophylactically administered SynthoPlate® was able to reduce blood volume loss by ~30%, reduced hypotension effects and increased survival by >80%. In pilot pig models of arterial bleeding, emergency administration of SynthoPlate® has shown substantial reduction in blood volume loss. Immunohistological evaluation of tissues from various treated animals have shown marked co-localization of red fluorescent SynthoPlate® with green fluorescent platelets localized at the clot site. Biodistribution studies in animals indicate that SynthoPlate® is cleared primarily by liver and spleen, similar to clinically known liposomal technologies. We have also demonstrated that the platelet-mimetic heteromultivalent surface-decoration approach can be adapted to other biomedically relevant particle platforms. Altogether, our studies establish the promise of SynthoPlate® nanotechnology as a platelet-mimetic intravenous hemostat for treatment of bleeding complications in prophylactic and emergency scenarios. Ongoing studies are focused on evaluating this technology in clinically motivated large animal bleeding models, with a vision for translation.

POLYMER DRUG CONJUGATES FOR THE DELIVERY OF SYNERGISTIC CHEMOTHERAPEUTICS

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BIOPOLYMERS FOR MEDICAL APPLICATIONS

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Biopolymers including alginate, chitosan, cellulose, cellulose acetate, silk, etc. that are used for the production of the biocomposite materials for applications in wound management will be presented. Optimized amount of active agents and model drugs, like eosin, PVPI, albumin, curcumin, essential oils of lavender, cinnamon, mint and others, can be incorporated into the biopolymer matrices. It will be presented the realization of smart fibrous mats, films from emulsions, and nanoparticles for wound dressings combining the abovementioned polymers derived from natural sources with the active agents. Electrospun fibers are excellent candidate for wound dressings and scaffolds, due to their characteristics of efficient absorption of wound exudates, gas permeability, protection against bacterial infections and oxidation, easy incorporation of bioactive molecules and drugs, good conformability, and promoted cell attachment and proliferation. Films from emulsions can combine hydrophobic biomatrices with hydrophilic drugs and vice versa, or can combine hydrophilic and hydrophobic drugs in one system. Finally, biocomposite nanoparticles or nanocapsules can be ideal candidates for reaching specific tissues or cells in the human body, which otherwise with conventional methods is very difficult. The controlled delivery in time of the active agents of these system will also be discussed.

ACTIVE NANOMATERIALS FOR BIOMEDICAL APPLICATIONS

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LASER WELDING AND REPAIR OF RUPTURED TISSUES USING PHOTOTHERMAL NANOCOMPOSITES

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BIOPOLYMER/NANOCOMPOSITE MATERIALS IN MEDICINE

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Key Words: Polymer nanocomposites, drug release, antibacterial, wound healing, gauzes

A large number of recent studies deal with the application of biopolymer nanomaterials to different medicinal applications that led to a new discipline known as nanomedicine. It comprises the processes of diagnosing, treating, curing, preventing diseases and also dealing with traumatic injury, relieving pain and preserving/improving human health by using nanoscale materials. Among nanoscale materials, an important place belongs to the group of natural and synthetic polymer nanocomposites. These are made up of an organic polymer matrix and mineral, organic or metallic nanofiller. The properties of polymer nanocomposites depend on the characteristics of the components and on the interaction polymer nanofiller. Polymer nanocomposites offer to modern medicine new opportunities for generate products. Hence, this talk will present recent advances in biomedical applications of nanostructured biopolymer nanocomposites including antibacterial treatments, tissue engineering, cancer treatment and drug delivery.

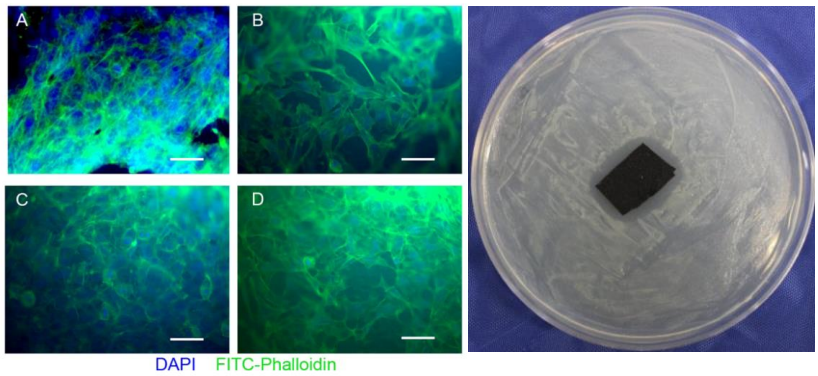

Figure 1 – A starch-based biopolymer composite rendered antimicrobial by functionalizing with another biopolymer. This smart biopolymer composite has no toxicity towards cell growth but is very effective against E-coli.

The multifunctional characteristics of polymer nanocomposites make them highly suitable for a wide range of applications in medicine. Some polymer nanocomposites can selectively deliver therapeutic and diagnosing agents specifically to a diseased site, some other are attractive for regenerative medicine applications (bones, nerves, vascular, muscles, etc.), diagnosing equipment, and so forth. The application of polymer nanocomposites in medicine can contribute beside other products, to saving lives and improving the life of a high number of people suffering from diseases. Progress in nanomedicine will undoubtedly require the close cooperation of multidisciplinary teams composed of biologists, bioengineers, physicians.

MIMICKING THE EXTRACELLULAR MATRIX – A BIOMATERIALS APPROACH TO INHIBIT TISSUE FIBROSIS

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Epithelial tissue is marked by the presence of a specialized, highly cross-linked, sheet-like extracellular matrix, the basement membrane. Tissue-invasive events, such as the epithelial-to-mesenchymal transition (EMT) - a key event in gastrulation, tissue fibrosis and cancer metastasis – are characterized by irreversible structural changes of the basement membrane through proteolytic processing by matrix metalloproteinases (MMPs). We have recently reported a previously unidentified laminin fragment that is released during EMT by MMP2 and that modulates key EMT-signalling pathways. Specifically, interaction of the laminin fragment with α3β1-integrin triggers the down-regulation of MMP2 expression, thereby constituting a cell-basement membrane-cell feedback mechanism. Inhibiting MMPs has been proposed as a strategy to prevent pathological cell migration and basement membrane breakdown in the course of EMT. Here, we explore this cell-matrix-cell feedback mechanism to target pathological EMT in the course of tissue fibrosis. We present an electrospun biomaterial that is functionalized with the recombinant laminin fragment and that can be directly interfaced with epithelial tissue to interfere with EMT pathways and inhibit MMP2 expression and activity in vitro and in vivo. We demonstrate how interaction of the functionalized synthetic membrane with peritoneal tissue inhibits mesothelial EMT in a mouse model of TGFβ-induced peritoneal fibrosis by decreasing active MMP2 levels, and propose a mechanism of how the laminin fragment acts downstream of α3β1-integrin in epithelial cells, after it is released from the basement membrane.

NANO/MESO-SCALE PRINCIPLES AND APPLICATIONS WITH FLEXIBILITY: FROM DELIVERY AND SELF-RECOGNITION TO DIFFERENTIATION

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From viruses to tissue matrices, biology is filled with remarkable polymeric structures that motivate mimicry with goals of both clarifying and exploiting biological principles. Filamentous viruses inspired our development and computations of worm-like polymer micelles – 'filomicelles' – that persist in the circulation and deliver even better than spheres [1]. However, particles of any type interact with innate immune phagocytes while nearby 'Self' cells are spared due to a polypeptide that limits phagocytic clearance [2]. The phagocyte's cytoskeleton forcibly drives the decision downstream of adhesion, proving analogous to how matrix elasticity directs stem cell fate [3, 4].

Key Words: block copolymer, self-assembly, shape, immunocompatability, differentiation

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DEVELOPING NANOSTRUCTURED THIN FILMS AS BIOMIMETIC TISSUE-ENGINEERED PLATFORM FOR CANCER RESEARCH

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Engineering *in vitro* models that reproduce tumor microenvironment and mimic functions and responses of tissues that is more physiologically relevant represents a potential bridge to cover the gap between animal models and clinical studies. In this talk, we describe nanostructured thin films as templates to develop biomimetic tissue-engineered technologies for cancer research. Our model systems enables us to examine the impact of dynamics changes in the physical environment of tumor microenvironment (TME) in conjunction to tumor-stromal (fibroblasts, mesenchymal stem cells (MSCs), immune cells) cell interactions to potentially mimic stable disease and/or its eventual progression to advanced stages. Tumors actively modulate their microenvironment by recruiting MSCs, lymphocytes and macrophages; vascular endothelial cells; and tumor-associated stromal cells such as fibroblasts. Tumor progression results in dynamic changes in the cell-cell interaction and tumor biology. Currently, the impact of key tumor-stromal cell interactions is unknown due to the lack of models or approaches that can address this key question.

In this study, we report a robust, inexpensive, protein free method that utilizes polyelectrolyte multilayers (PEMs) and capillary force lithography (CFL) to generate patterned co-culture models of breast cancer cells and stromal cells. PEMs have been shown to be excellent candidates for biomaterial applications. In our study, we used synthetic polymers, namely poly(diallyldimethylammoniumchloride) (PDAC) and sulfonated poly(styrene) (SPS) as the polycation and polyanion, respectively, to build the multilayers. We as well others have previously shown that PEM surfaces utilizing PDAC and SPS also provide an ability to control the arrangement of multiple cell types with subcellular resolution. This technique allows the formation of cell patterns with different shapes and sizes of tunable directional properties, recreating cell-cell interactions in a highly controlled manner. In this study, we capitalized upon the differential cell attachment and spreading of breast cancer cells on different PEM surfaces to engineer patterned co-cultures of breast cancer cells and stromal cells. To demonstrate the translational validity of our platform, we employed two developmentally distinct human breast cell lines for co-culture development: 1) BT474 (HER2+ invasive breast cancer cells to model invasive ductal carcinoma (IDC)), and 2) 21MT-1 (stable patient-derived metastatic breast cancer cells isolated from the metastatic pleural effusion to model invasive mammary carcinoma (IMC)). We also used two different types of stromal cells, mammary epithelial cells (MCF10A) and mesenchymal stem cells (MSCs) to demonstrate the versatility of our platform. Since MCF10A are non-tumorigenic cells and MSCs have a significant role in metastasis, our platform provides an opportunity to study cell-cell interactions in a heterogeneous TME, an inimitable property of cancer progression. We further illustrated that our *in vitro* breast tumor model is capable of staging the breast tumor dynamics and emulating clinical relevant molecular pathways at different stages of tumor points. For this purpose, we utilized the co-culture system developed in this study and demonstrated that our platform simulated key clinical markers prominently used for tumor diagnosis, including tumor (HER-2) and proliferation (Ki67) markers. Also our platform mirrored the clinical conditions when probed for miRNA-21 and miRNA-34 expression. The development of such *in vitro* models that recapitulates the *in vivo* like signaling in tumor would be desirable to increase the drive towards precision medicine to identify key biomarkers for early diagnosis and novel therapeutic interventions.

MODELING THE TUMOR MICROENVIRONMENT WITH NANOSTRUCTURED MATERIALS

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The complex microenvironment in a solid tumor is a major barrier in understanding the molecular and mechanical mechanisms that control cancer progression. Biophysical approaches used to quantify the intracellular forces from the actin cytoskeleton and surface traction forces from adhesion allow us to probe the biomechanical properties of individual cells with an unprecedented level of detail. By systematically investigating the parameters in the tumor microenvironment that control cancer cell behavior, as well as their interactions with tumor-associated stromal cells, we hope to gain a better understanding of malignant cell behavior. Toward this end, my lab has developed a high-content mechanomic screening approach to simultaneously profile forces exerted by cells in the tumor on the underlying matrix, along with a number of other cell variables (including morphology, motility, growth, and apoptosis) important in cancer progression. Cells are seeded on synthetic and natural biomaterials engineered to mimic different aspects of human tissues. My presentation will focus on lessons we've learned from modeling the tumor microenvironment with these nanostructured materials.

NANO AND MICROPARTICLES AS THERANOSTIC AGENTS

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BIOINSPIRED CHIRAL SUPRAMOLECULAR HYDROGELS

Chuanliang Feng, Shanghai Jiao Tong University, China

CELL-ECM INTERACTIONS AND THEIR RELEVANCE TO CANCER

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Perturbed microenvironmental conditions play important roles in tumor initiation, progression, and therapy response; however, the underlying molecular, cellular, and tissue-level mechanisms remain relatively poorly understood. By integrating biomaterials, tissue engineering, and microfabrication strategies our lab has developed a variety of *in vitro* and *in vivo* models to study tumorigenesis under pathologically relevant conditions. In particular, we are applying these model systems to evaluate the regulatory roles of extracellular matrix (ECM) physicochemical properties on tumor-stroma interactions with a focus on tumor angiogenesis and metastasis. This talk will summarize some of our efforts in this area and discuss tumor-mediated differences in ECM physicochemical properties, and the resulting functional consequences on tumor cell behavior.

ASSEMBLY AND FUNCTION OF FIBROBLAST-DERIVED EXTRACELLULAR MATRICES

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For a tumor to develop and spread, the growth-repressive environment of the host tissue must undergo significant changes. These changes include dramatic modifications in the molecular composition and architecture of the extracellular matrix (ECM). Importantly, different tumors have distinct ECM components, depending on their anatomical site. Accordingly, differences can exist between the ECM of primary tumors and metastatic lesions. The ECM can impact treatment, including the efficacy of resection and accessibility of solid tumors to therapeutic antibodies and small molecules. Conversely, treatment can impact the ECM (e.g. radiotherapy, platinium-based drugs) by promoting the deposition of a dense fibrotic stroma.

My laboratory seeks to unravel the cell-dependent mechanisms that drive matrix assembly, and to improve our understanding of the functional interplay between tumor cells and their matrix microenvironment. The tumor ECM is largely synthesized and remodeled by stromal fibroblasts. I will discuss our characterization of matrices produced by head and neck tumor-associated fibroblasts and discuss how these fibrillar networks enriched in so called “oncofetal” matrix proteins convey specific biological signals to the cells they encounter.