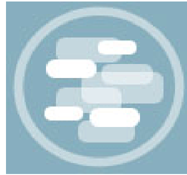
PROGRAM



ASME 2018 NEMB

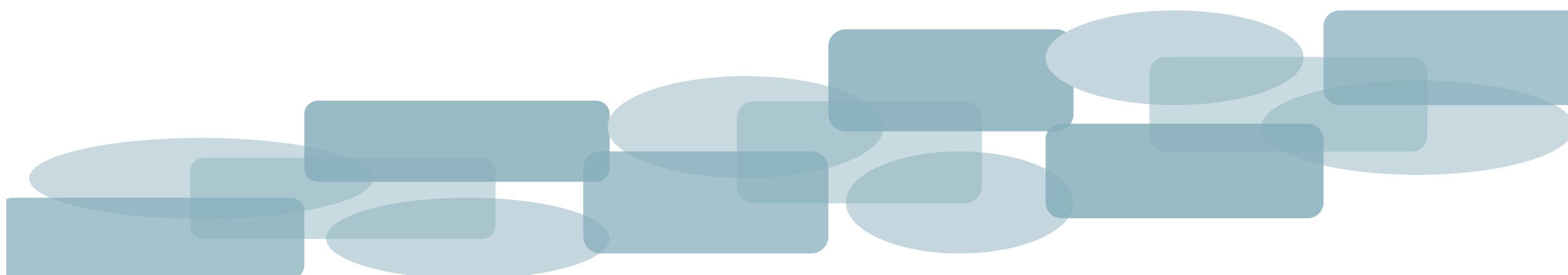
NanoEngineering for Medicine and Biology Conference

Conference | August 21-24, 2018

Exhibition | August 22-23, 2018

OMNI Los Angeles Hotel,

California Plaza,
Los Angeles, CA



TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-1
MICRO/NANOTECHNOLOGY FOR THERAPEUTICS DELIVERY
Los Angeles, OMNI Hotel, Museum A
2:00pm - 3:20pm

Session Organizer: **James Moon**, *University of Michigan, Ann Arbor, MI, United States*

Advanced Functional Magnetic Glyconanoparticles for Atherosclerosis Detection
Keynote. NEMB2018-6139

Xuefei Huang, Seyedmehdi Hossaini Nasr, Chunqi Qian, *Michigan State University, East Lansing, MI, United States*

Carbohydrates are ubiquitous in nature. They play important roles in many biological functions. In this talk, we will present our work in combining biological recognition of a carbohydrate, i.e., hyaluronan (HA), with the properties of magnetic nanoparticles for the detection of vascular inflammation and atherosclerosis.
Cardiovascular diseases, often associated with inflammation and atherosclerosis, are the leading cause of death and disability in the world. Despite the significant progress in recent years, there remain large unmet needs to detect vulnerable atherosclerotic plaques, which are prone to ruptures subsequently causing heart attacks and strokes. CD44 is a cell surface receptor, which has been shown by multiple studies to promote atherosclerosis by mediating inflammatory cell recruitment and vascular cell activation. Moreover, the expression of CD44 is up-regulated more than ten folds at rupture prone vascular sites, thus presenting an attractive target for molecular imaging. HA is a major endogenous ligand of CD44. In order to detect the presence of CD44 in atherosclerotic plaques, we have synthesized magnetic nanoparticles coated with HA. However, significant inflammatory responses were observed when macrophages were incubated with these nanoparticles. Interestingly, we discovered that engineering of the shape of the nanoprobes can significantly reduce the inflammatory properties of the probes. The new nanoprobes have high relaxivities, which are suitable contrast agents for magnetic resonance imaging. The results on non-invasive in vivo detection of atherosclerotic plaques in a clinically relevant model of ApoE knockout transgenic mice aided by these HA functionalized nanoprobes will be presented.

Discrete, Bio-compatibilized Carbon Nanotubes Demonstrate High-efficiency Membrane Transport for Therapeutics and Enable Bone-Targeted Drug Delivery in Burkitt's Lymphoma Model
Technical Presentation. NEMB2018-6127

Carolyne Falank, *Maine Medical Center Research Institute, Scarborough, ME, United States*, ***Aaron Tasset***, *Biopact, Austin, TX, United States*, ***Sophie Harris, Mariah Farrell***, *Maine Medical Center Research Institute, Scarborough, ME, United States*, ***Milos Marinkovic***, *Biopact, Austin, TX, United States*, ***Michaela Reagan***, *Maine Medical Center Research Institute, Scarborough, ME, United States*

Carbon nanotubes (CNTs) hold great potential as drug delivery vehicles due to their unique architectural properties, large loading surface area and tunable chemistry. Unfortunately, clinical translation of CNTs has been inhibited by toxicity, both in cell culture and animal models, resulting from poor physiological solubility/clearance and the presence of residual contaminants.

XACTTM is a novel delivery technology that aims to overcome obstacles to the effective utilization of CNTs in biological systems. Here, we demonstrate that chemically-functionalized, purified, discrete CNTs (dCNTs) yield bio-compatibilized and highly-stable delivery vehicles with predictable properties and performance. In addition, we provide evidence that in vivo biodistribution of dCNTs is tunable by altering physical and chemical properties.

Stability and nontoxicity of dCNTs are essential for successful utilization in biological systems. Long-term colloidal stability of dCNTs was evaluated by analyzing zeta potential (-40 to -50 mV) and physiological compatibility was optimized for ionic, high-serum environments. Cytotoxicity of dCNTs was evaluated in several murine and human cell-types, including prostate and myeloma cancer cell lines, as well as normal MSCs. Critically, dCNTs were found not found to elicit cytotoxicity in therapeutically-relevant concentrations. In order to investigate the transmembrane transport potential, LNCaP cells were treated with dCNTs loaded with KLAKLAK, a pro-apoptotic peptide incapable of diffusion across the cellular plasma membrane. Following 72-hour incubation, cells treated with peptide alone or unloaded dCNTs remained viable, while no cells remained in groups treated with dCNTs loaded with the apoptotic ligand. These findings demonstrated feasibly for in vivo drug delivery studies, as they established that dCNT endocytosis is non-cytotoxic and dCNT-loading does not alter biological functionality of payload. an vivo toxicity was investigated in a murine model by intravenous administration. dCNTs were well-tolerated and achieved a high MTD of 70 mg/kg. Biodistribution studies were conducted with two unique formulations of liver- and bone-targeting dCNTs using radioisotope labeling. Approximately 60% of injected dCNTs from each formulation trafficked to their physiological target, while other fractions demonstrated clearance from various organs.

We next evaluated the potential of bone-targeting dCNTs for therapeutic delivery in a murine Raji-Burkitt?s lymphoma model. Whole-body bioluminescence imaging revealed that, similarly to treatment with free Dox, the group receiving Dox-loaded, bone-targeting dCNTs showed significantly reduced tumor burden. In addition, this group demonstrated increased survival compared to free Dox and untreated controls. Typical indications of Dox-induced toxicity, such as rapid weight loss and/or drug-related mortality, were not observed in mice receiving Dox-loaded dCNTs, confirming the potential of site-specific delivery to reduce chemotherapy-associated morbidities.

In summary, XACTTM dCNTs are stable, nontoxic and versatile delivery vehicles, featuring a promising capability for targeted delivery to cells, organs and tissues. This novel technology offers considerable clinical potential as a therapeutic delivery mechanism for bone and liver diseases, but is also suitable for bio-industrial processes such as intracellular gene transport in agricultural engineering.

Delivery of Docetaxel to Breast cancer cells Employing Water Soluble Carbon Nanotubols: Enhanced Anti-neoplastic activity and Improved Pharmacokinetic Profile
Technical Presentation. NEMB2018-6105

Nagarani Thotakura, Kaisar Raza, Vipin Kumar, *Central University of rajasthan, KISHANGARH, Rajasthan, India*

In the present research, the aim was to synthesize aspartic acid tagged water soluble CNTnols and to deliver docetaxel to cancer cells with enhanced safety and efficacy. Various characterization studies like FT-IR and NMR spectroscopy were performed after synthesizing Docetaxel conjugated aspartic acid derivatized CNTnols. Particle size analysis, zeta potential, PDI and FE-SEM were also used for characterization of nanoconjugate. Release kinetics, cytotoxicity assay, cellular uptake studies and pharmacokinetics and other methods were used for evaluation of conjugate. From cell viability studies, it was found that there was 4.05 times decrease in IC50 values after conjugation showing the targeted action. Cellular uptake studies are in support with cytotoxic studies proving the enhancement in cellular uptake of docetaxel. Through pharmacokinetic studies it was observed that the half-life and bioavailability was increased by 6 and 4.3 times when compared to pure drug. It was found that the synthesised nanoconjugate was hemocompatible and offered low protein binding. All the findings are promising in nature and the nanoconjugate was considered as a novel carrier for delivery of anti-cancer drugs, especially belonging to BCS class IV.

Antibacterial Studies of Zinc Oxide Nanoparticles Assisted with Femtosecond Laser Light
Student Competition Presentation. NEMB2018-6201

Crysthal Alvarez, *University of California, Riverside, San Bernardino, CA, United States*, ***Natanael Cuando, Guillermo Aguilar***, *University Of California, Riverside, Riverside, CA, United States*

Cranial implant infections represent a major therapeutic challenge as the blood-brain barrier inside the skull excludes most conventional drugs used to treat infections. A new approach of a transparent ceramic cranial implant comprised of Yttria Stabilized Zirconia brings the possibility of new treatments for bacterial infections. This implant will provide optical access to the brain and being transparent will allow for non-invasive laser-based treatments. In this study, we investigate Zinc Oxide (ZnO) nanoparticles and femtosecond laser light independently, alternatively, and combined. The nanoparticles are used as a bactericidal agent and the femtosecond laser light as an activator agent. The ZnO nanoparticles interact with this kind of laser light in a non-linear fashion. One of the non-linear optical effects is multi-photon emission to induce redox species and combat infection, and second harmonic generation, which could be used for optical imaging in the future. For this study, a femtosecond pulsed laser at 1030 nm, 54 MHz, and pulse duration of 250 fs were used to irradiate a overnight cultures of Escherichia coli (E. coli) grown in Luria-Bertani (LB) broth. Bacterial solutions with and without ZnO nanoparticles were studied. Cultures of E. coli with no treatment, meaning no nanoparticles and no laser irradiation, were used as a control. Solutions with and without ZnO nanoparticles were plated in a 48 well plate and placed on a hot plate to perform laser irradiation from 15 to 60 minutes. Following the irradiation, the samples were incubated for 20 hours at 37°C. All solutions were then diluted and plated onto agar plates. As expected, the minimum number of colony forming units per milliliter presented at the longest irradiation time period tested. When comparing the laser-assisted ZnO nanoparticles treatment with its non-irradiated counterpart, one can see that laser light clearly enhances the antibacterial activity of ZnO nanoparticles. Our studies suggest that the use of ZnO nanoparticles inhibit bacterial growth. Laser irradiation treatment alone also offers inhibition of bacterial growth, up to 70%. The incorporation of ZnO nanoparticles offers an additional 20% inhibition. Antibacterial activity of ZnO has been reported in literature, however, our study shows the combination of ZnO nanoparticle on the implant and femtosecond laser light has a greater growing inhibition of Escherichia coli (E. coli). ZnO nanoparticles as a coating material on this transparent implant is ongoing work.

TRACK 3
Nano/micro biomechanics and mechanobiology

Track Organizer: **Anna Grosberg**, *University of California, Irvine, Irvine, CA, United States*
Track Co-Organizer: **Mohammad Mofrad**, *Univ of California, Berkeley, Berkeley, CA, United States*

3-1
MOLECULAR SCALE INSPIRED BIOMECHANICS
Los Angeles, OMNI Hotel, Hershey Room
2:00pm - 3:20pm

Session Organizer: **Wonmuk Hwang**, *Texas A&M University, College Station, TX, United States*
Session Co-Organizer: **Jonathan Choi**, *The Chinese University of Hong Kong, Shatin, Hong Kong*

How does the motor protein kinesin burn its fuel?
Keynote. NEMB2018-6185

***Wonmuk Hwang**, Texas A&M University, College Station, TX, United States*

Kinesin is the smallest known motor protein that can walk processively. It hydrolyzes one adenosine triphosphate (ATP) molecule as a fuel to make an 8-nm step on the microtubule track, generating up to 5-7 pN of force. The atomistic mechanism by which kinesin handles ATP during its motility was largely unknown. To address this question, we performed multi-microsecond molecular dynamics simulation of the kinesin-microtubule complex in different nucleotide states. We find each of the fuel processing events - ATP binding, hydrolysis, and release of hydrolysis products - is mediated by mobile subdomains around the ATP binding pocket, in particular, the switch-I domain: An ATP near kinesin is actively captured by the mobile `trio' domains that act like a 3-pronged antenna; hydrolysis of ATP is mediated by dynamic coordination of catalytic water molecules while ATP is torsionally strained; release of hydrolysis products (inorganic phosphate and adenosine diphosphate, ADP) is also assisted by switch-I pulling them.
These highlight the essential role of conformational dynamics for kinesin motility. Since residues of kinesin that directly contact ATP are highly conserved, varying the mobility of the subdomains is likely utilized for fine-tuning kinetic rates of ATP processing and thereby controlling the motility characteristics of different kinesin families.

Understanding Receptor-Mediated Endocytosis of Elastic Nanoparticles Through Coarse Grained Molecular Dynamic Simulation
Technical Presentation. NEMB2018-6112

***Ying Li**, University of Connecticut, Storrs, CT, United States*

For nanoparticle (NP)-based drug delivery platforms, the elasticity of NPs has significant influence on their blood circulation time and cellular uptake efficiency. However, due to the complexity of endocytosis process and inconsistency in the definition of elasticity for NPs in experiments, the understanding about the receptor-mediated endocytosis process of elastic NPs is still limited. In this work, we developed a coarse-grained molecular dynamics (CGMD) model for elastic NPs. The energy change of elastic NPs can be precisely controlled by the bond, area, volume and bending potentials of this CGMD model. To represent liposomes with different elasticities, we systematically varied the bending rigidity of elastic NPs in CGMD simulations. Additionally, we changed the radius of elastic NPs to explore the potential size effect. Through virtual nano-indentation tests, we found that the effective stiffness of elastic NPs was determined by their bending rigidity and size. Afterwards, we investigated the receptor-mediated endocytosis process of elastic NPs with different sizes and bending rigidities. We found that the membrane wrapping of soft NPs was faster than stiff ones at early stage, due to the NP deformation induced large contact area between the NP and membrane.
However, because of the large energy penalties induced by the NP deformation, the membrane wrapping speed of soft NPs slows down during the late stage. Eventually, the soft NPs are less efficient than stiff ones during the membrane wrapping process. Through systematic CGMD simulations, we found a scaling law between the cellular uptake efficiency and phenomenal bending rigidity of elastic NPs, which agrees reasonably well with experimental observations. Furthermore, we observed that membrane wrapping efficiencies of soft and stiff NPs with large size were close to each other, due to the stronger ligand-receptor binding force and smaller difference in stiffness of elastic NPs. Our computational model provides an effective tool to investigate the receptor-mediated endocytosis of elastic NPs with well controlled mechanical properties. This study can also be applied to guide the design of NP-based drug carriers with high efficacy, by utilizing their elastic properties.

Uptake of sub-25 nm nanoparticles by cells under defined levels of compression
Technical Presentation. NEMB2018-6107

***Hongrong Yang, Jonathan Choi**, The Chinese University of Hong Kong, Shatin, Hong Kong*

Many investigations into the interactions between nanoparticles and mammalian cells entail the use of culture systems that do not account for the effect of extracellular mechanical cues, such as compression. In this work, we present an experimental set-up for systematically investigating the combined effects of nanoparticle size and compressive stress on the cellular uptake and intracellular localization of poly(ethylene glycol)-coated gold nanoparticles (Au-PEG NPs). During cellular uptake, we employ an automated micromechanical system to impose defined levels of uniaxial compressive strain (between 0.05 and 0.4) to a porous agarose gel, which in turn transmits defined levels of unconfined compressive stress (between 70 Pa and 200 Pa) to C2C12 myoblasts that are seeded underneath the gel. Upon 140 min of compression, a duration of time insufficient to inflict obvious injury to the cells, uptake of Au-PEG NPs smaller than 25 nm by compressed myoblasts is up to 5-fold higher than that by uncompressed cells. The optimal compressive stress for maximizing the cellular uptake of sub-25 nm NPs monotonically increases with NP size. With and without compression, sub-25 nm Au-PEG NPs enter cells via energy-dependent uptake; they also enter compressed C2C12 myoblasts via clathrin-mediated endocytosis as the major pathway. Upon cellular entry, the Au-PEG NPs more readily accumulate in the late endosomes or lysosomes of compressed cells than uncompressed cells. Results from our experimental set-up yield mechanistic insights into the delivery of NPs to cell types that experience extracellular compression under physiological conditions.

A Multiscale Investigation of Mechanical Properties of Bio-inspired Scaffolds
Student Competition Presentation. NEMB2018-6259

***Yucong Gu, Mohan Yasodharababu, Arun Nair**, University of Arkansas, Fayetteville, AR, United States*

Bone implants require high porosity and large pore size to allow new bone to form. However, scaffolds with such properties tend to have reduced mechanical strength. Thus, finding a structural design which allows the implant to have a high porosity and large pore size while retaining high strength is essential.

In this research, a bio-inspired scaffold based on the observed geometrical pattern of the apatite (HAp) atomic crystal structure, along with other common geometric patterns of scaffold structure, are designed and analyzed using a multiscale computational approach. Material properties are found using the density functional theory calculations; which in turn is used to find the stress under different loading conditions for the scaffolds using finite element analysis (FEA). Results show that the HAp-inspired scaffold structure reduces the maximum stress concentration compared to other scaffold geometries studied here; therefore, it is less likely to fail. Due to substitutions during aging, the scaffolds made of apatite can be significantly different from stoichiometric HAp. Hence, we investigate the effects of different substitutions. This study provides an insight into a better scaffold design from bio-inspired structures and the effect of substitutions on HAp generated scaffolds.

TRACK 5
Nano biosensors for molecular analysis

Track Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*
Track Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

5-1
NANOSTRUCTURED SENSORS FOR CELL ANALYSIS
Los Angeles, OMNI Hotel, Bradbury Room
2:00pm - 3:20pm

Session Organizer: **Bianxiao Cui**, *Stanford University, Stanford, CA, United States*
Session Co-Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*

Nanoscale electrodes for intracellular electrophysiological recording
Keynote. NEMB2018-6263

***Bianxiao Cui**, Stanford University, Stanford, CA, United States*

The close distance between the cell membrane and the measuring electrode is crucial for sensitive measurement of cell electric activities. We are interested in exploring nanotechnology and novel materials to improve the membrane-electrode coupling efficiency. Recently, we and other groups show that vertical nanopillars protruding from a flat surface support cell survival and can be used as subcellular sensors to probe biological processes in live cells. The nanopillar electrodes deform plasma membrane inwards and induce membrane curvature when the cell engulfs them, leading to a reduction of the membrane-electrode gap distance and a higher sealing resistance. As an electrode sensor, nanoelectrodes offer several advantages such as high sensitivity, subcellular spatial resolution, and precise control of the sensor geometry. We found that the 3D topology of nanopillars is crucial for its enhanced signal detection. The high membrane curvature induced by vertical nanopillars significantly affects the distribution of curvature-sensitive proteins and stimulates several cellular processes in live cells. Our studies show a strong interplay between biological cells and nano-sized sensors, which is an essential consideration for future development of interfacing devices.

Plasmonic protein marker detection based on single nanoparticle swarm sensing
Technical Presentation. NEMB2018-6106

***Mengxing Ouyang, Dino Di Carlo**, University of California, Los Angeles, Los Angeles, CA, United States*

Conventional spectrum-based detection upon binding of analytes to metallic nanoparticles measures the spectral shift with a spectrometer, which relies on the averaged signal from a localized ensemble of particles without rigorous control of the sensor conditions, this approach may fall short for accurate and robust detection in complex biofluids in clinical settings.
We demonstrate a nanoplasmonic biosensor with readout based on the shift in hue for a large distribution of single nanoparticles (a nanoparticle swarm) which yields improved robustness to assay conditions compared to conventional approaches.
The sensor surface is composed of a multitude of monodispersed gold nanoparticles (AuNPs) spread over an optically transparent surface, where a few hundreds to over a thousand single nanoparticles are interrogated within one imaging field of view, enabling the analyses of a few thousands of individual readouts for each device. For nanoplasmonic detection, we use a color camera to monitor the hue change of each nanoparticle by extracting the individual RGB information from dark field images before and after the binding events. In order to operate with a cost-effective optical system, we design the pair of capture and detector AuNPs to generate a large hue shift from green to orange that is easily detected.
Our swarm sensing platform with capture AuNPs immobilized on a glass substrate exhibited a large dynamic range (at least 4 orders of magnitude) with a limit of detection of 1nM in buffer solution, and further demonstrated successful detection of c-reactive protein in human serum with quantitative accuracy in the 3-tier clinical cutoff range (1-10μg/ml) without the need for a blocking step. Comparison analyses of readout using final states of the hue revealed that swarm sensing using the change in hue for each particle as metric renders the platform tolerant to both particle and device variation with minimal interference from non-specific binding. In addition, the informative sensing scheme enables the mapping of detection performance of each single nanoparticle versus its initial state, which provides further capabilities to identify optimal sensors in the swarm during data analyses.
In summary, different from conventional approaches, our swarm sensing approach recognizes individual signal shifts from a large population of single particles, and therefore achieves more consistent overall sensor readout. The simplicity and cost-effectiveness of the optical readout instrumentation and microfluidic device allow future adaptation to nanoplasmonic point-of care assays with handheld darkfield readers. In addition, the nanoparticle preparation approach suggests the flexibility for platform multiplexing.

Enhancement of Piezoelectric Signal from BaTiO3-composite Microneedle Biosensors using Finite Element Analysis
Technical Presentation. NEMB2018-6137

***JIYONG LEE, YEJIN LEE, SEOYUN LEE, KANGJU LEE, WONHYOUNG RYU**, YONSEI University, SEOUL, Korea (Republic)*

Human mortality and morbidity are profoundly affected by the mechanical failure of biological tissue. It is important to precisely measure the changes of mechanical properties of living tissue such as stiffness or viscoelasticity. BaTiO3, a biocompatible piezoelectric ceramic which can generate piezoelectric potential under external stress, has been widely investigated and composed with other biomaterials to fabricate biomechanical sensors. However, for continuous detection of local and subtle changes of constantly moving living tissue, sensors should be flexible, highly sensitive, and able to maintain contact on the tissue all the time. For these reasons, we have developed a flexible BaTiO3-composite microneedle (MN) array as a piezoelectric sensor and analyzed material properties of MNs for enhancement of its sensitivity using finite element method (FEM). The 5 x 6 composite MN array with the height of 640 um was micro-molded using the mixture of BaTiO3, CNT, and PDMS at a ratio of 12: 1: 87 (w/w). In order to get flexibility, PDMS was selected as a a main component of the MNs to have similar strength to the biological tissue, and CNT was used as a dispersant. 50 nm of Pt electrodes were deposited at the top and bottom of the MN structures to collect piezoelectric signals from MNs. Subsequently, 1 um^3 of unit cell composed of 27 BaTiO3 nanoparticles with the radius of 100 nm was designed and simulated using the COMSOL Multiphysics to understand a relationship between the magnitude of mechanically generated potential and the direction of external stress of the electrically polarized MNs. For the setting of the poling direction to improve the piezoelectric signal of the MNs, 1 MPa of external stress was applied to the unit cell which was polarized to z-axis direction and the FEM results showed internal potential difference. The magnitude of potential difference generated in the unit cell was improved depending on the direction of the external stress. The internal potential difference increased twice when the stress was applied to the same direction (1217 uV) with polarization than the x- (582.8 uV) and y- (597.9 uV) axes. The results indicated that MNs sensor could generate increased potential when the poling direction and deformation was set in the same way. According to the results of simulations, MN sensor was electrically poled to z-axis direction with 500 V at 135 °C for 12 h. Finally, piezoelectric signal from the MN sensors during deformation was recorded in real time using a voltmeter. Consequently, the peak magnitude of recorded potentials from MNs sensor has doubled after poling in the same direction as the deformation.

Measuring Protein Secretion From Single Cells at Single Molecule Resolution Using Quantum Dots
Technical Presentation. NEMB2018-6115

***Vanessa Herrera, Ssu-Chieh Joseph Hsu, Maha Rahim**, UC Irvine, Irvine, CA, United States, **Wendy Liu**, University of California Irvine, Irvine, CA, United States, **Jered B. Haun**, University of California, Irvine, Irvine, CA, United States*

Single cell analysis methods are becoming increasingly important since understanding how individual cells process information and respond to stimuli could lead to greater insight into various disease states. A single cell behavior that has received limited attention is protein secretion.
Soluble proteins play a critical role in controlling cell population behavior, but directly monitoring cell secretion is technically challenging. To address this issue, single cell arrays have been developed that isolate single cells in microwells. The wells are then covered with a glass slide containing immobilized antibodies to capture proteins secreted by individual cells, followed by removal of the glass slide and quantification by immunofluorescence. While this platform has proven powerful, a current limitation is that detection sensitivity is only in the ng/ml range (~10 pM) for most proteins. Thus, increasing detection sensitivity would significantly improve this already powerful analysis technique by enabling interrogation at earlier time points or in response to more subtle activation factors. Nanomaterial probes have been shown to provide remarkable detection capabilities in cell-based detection applications; especially luminescent quantum dots (QD), with their bright and photostable signals. In this study, we used QD in a sandwich immunoassay with imaging optimized to detect single QD point sources of light to achieve a detection sensitivity of 3 fg/ml (180 aM) for TNF-alpha soluble protein. When compared to immunofluorescence detection, the QD based platform is ~10^6-fold more sensitive in standard sandwich immunoassays. The QD detection scheme was also used in single cell secretion studies using PMA differentiated and LPS activated U-937 cells. We found that our QD-based detection method increased the number of single cells that could be interrogated for TNF-alpha secretion by 3-fold relative to a traditional organic fluorophore, improving detection threshold from 30 pM or 10,000 TNF-alpha molecules down to only 5 fM or 2 molecules. Based on these findings, our QD point source imaging technique nearly maximizes the detection sensitivity of single cell secretion studies. In future work, we will use this technique to assess the dynamics of immune cell secretion under diverse activating stimuli and in populations obtained from diseased tissues such as solid tumors. We will also incorporate multiplexing capabilities.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-2
MICRO/NANOTECHNOLOGY FOR DIAGNOSIS, PROGNOSIS, AND DRUG DELIVERY
Los Angeles, OMNI Hotel, Museum B
3:30pm - 4:50pm

Session Organizer: **Rafael Davalos**, *Virginia Tech, Blacksburg, VA, United States*

Quantum Diagnostics: from single-cells to single-molecules
Keynote. NEMB2018-6138

***Dino Di Carlo**, University of California, Los Angeles, CA, United States*

The ultimate limits of sensitivity in measuring biological systems occurs at the level of single-cells and single-molecules. I will discuss our approaches leveraging microfluidic and microfabrication technologies to interface at the scale of these single entities. In particular, we make use of the ability to compartmentalize fluid volumes to a sub-nanoliter scale and manipulate cells using unique microscale physics. I will discuss progress in using these quantized or digital measurements towards new diagnostics in monitoring immune system dysfunction, characterizing the invasive state of circulating tumor cells, and screening for drugs that modulate the contractile forces that single muscle cells apply.

HINT1 REGULATED SELF-ASSOCIATION OF NUCLEOSIDE PHOSPHORAMIDATE FUNCTIONALIZED SUPRAMOLECULAR NANOFIBERS
Student Competition Presentation. NEMB2018-6135

***Harrison West**, University of Minnesota, Columbia Heights, MN, United States*, ***Carston Wagner, Clifford Csizmar**, University of Minnesota, Minneapolis, MN, United States*

The non-covalent association of molecules is a ubiquitous feature of life. Protein scaffolds, components of the extracellular matrix, and even duplexed nucleic acids all undergo supramolecular assembly. To generate synthetic self-assembled nanostructures, a wide variety of small molecule motifs have been developed that utilize hydrogen bonding, electrostatics, and hydrophobic interactions to contribute to the assembly process. Growing interest in the regulation of supramolecular assembly has produced a variety of responsiveness motifs. The governing effect of these motifs is exerted through physical and chemical cues such as ultrasound, temperature, pH, reduction and oxidation, and enzymatic responsiveness. Enzymes are ideal for the regulation of supramolecular interactions as they allow the mimicry of biological systems. They are catalytic in nature, able to be regulated by various biomolecules and ligands, and are biocompatible.
To create a responsive and tunable self-assembly system, we have developed Histidine Triad Nucleotide Binding Protein 1 (HINT1) responsive nucleoside phosphoramidate pro-gelators (PPGs). HINT1 has been well characterized as a nucleoside phosphoramidase and acyl-adenylate hydrolase. At PPG concentrations above the critical micelle concentration and below the gelation point, these molecules assemble into highly regular nanofibers resulting in bulk viscous liquid formation. Utilizing HINT1, the self-assembling peptides may be released from the blocking effect of nucleoside phosphoramidate moieties which induces the soluble nanofibers to condense into highly associated nanofiber bundles observed by electron microscopy. The structural transition to nanofiber crosslinking at the nanoscale results in bulk material gelation. We have utilized chemical biological tools in conjunction with small amplitude oscillatory rheometry to further characterize the role of HINT1 in the observed gelation event. Small molecule inhibitors and catalytically dead HINT1 mutants were used to investigate the role of HINT1 active site and catalytic activity on the regulation of PPG assembly. Inhibitors have been shown to block HINT1 activity on PPG substrates, and Hint1 H112N catalytically dead mutant has been shown to be unable to activate self-assembly. Our goal is to develop an adaptable system for the construction of biologically responsive materials that may be assembled in situ in response to HINT1 activity.

Shape dependent transport of micro-particles in blood flow: from margination to adhesion
Technical Presentation. NEMB2018-6111

***Ying Li**, University of Connecticut, Storrs, CT, United States*

We explore the shape effect of micro-particles (MPs) on their margination behaviors in blood flow through three-dimensional numerical simulations. Eight different shapes of MPs are considered with identical volume, such as sphere, rod, cubic, disk, oblate and prolate with different aspect ratios. These MPs are immersed in the blood plasma, which is consists of suspension of RBCs. A simple shear flow is applied with moderate shear rate (200/s). The fluid flow and immersed particles (RBCs and MPs) are solved by the Lattice Boltzmann method (LBM) and spring-lattice model, respectively. The fluid-structure interaction is coupled by immersed boundary method. Additionally, we adopt a stochastic model to capture the adhesive behavior of MPs near the vessel wall for ligand-receptor binding. Without near-wall adhesion, the spherical particle demonstrate the strongest margination in the blood flow. It can be attributed to the large collision displacement with RBCs and small migration distance in cross-stream direction under shear flow of spherical particles. Furthermore, under the influence of near-wall adhesion, the margination of different shaped MPs is examined. Interestingly, the adhesion can either promote or impede the margination behavior depending on the shapes of MPs. When the major axes of MPs is smaller than or comparative to the thickness of the cell-free layer in the flow channel, the adhesion can promote margination of these MPs. While for MPs with large major axes, due to the near-wall adhesion effect, the reduce tumbling frequencies enable them to have enough time to interact with RBCs. In turn, the long time interaction with RBCs can drag these MPs to the central stream of blood flow, impeding their margination. However, the prolate particles demonstrate distinct behaviors. Apart from tumbling, the transition to precession of prolate particles near the vessel wall results in the enhancement of margination. Overall, the sphereical MP outperform other non-spherical MPs for its high margination propensity under the influence of near-wall adhesion and moderate shear flow rate. This study might offer theoretical guidance to design MP-based drug carriers in blood flow with high efficacy.

Nanowire Labeling System using Ferromagnetic Resonance
Student Competition Presentation. NEMB2018-6167
***Joseph Um, Wen Zhou, Yali Zhang, Daniel Shore, Rhonda Franklin**, University of Minnesota, Minneapolis, MN, United States*, ***Bethanie Stadler**, Univ Of Minnesota, Minneapolis, MN, United States*

Current methods for treating cancer often destroy both unhealthy and healthy cells. So, it is important to distinguish unhealthy cells from healthy cells for more accurate diagnosis and better treatment in the near future. In this work, we have developed a magnetic nanowire labeling system that can be used to identify many cell types using engineered ferromagnetic resonance (FMR) to produce unique signatures. The magnetization precession frequency of a ferromagnetic material can be controlled with an applied DC magnetic field in accordance with the Kittel equation. The material will absorb energy from nearby ac magnetic fields that match this frequency. Here, Ni, Fe, and Co nanowires were made by template-directed electrodeposition. The nanowire lengths were measured by scanning electron microscopy (20um, 24um, 29um), and saturation magnetizations were measured by vibrating sample magnetometry (0.6T, 2.1T, 1.8T) for Ni, Fe, and Co nanowires, respectively. The nanowires were then placed onto a coplanar waveguide to apply a fixed microwave frequency in a sweeping DC magnetic field parallel or perpendicular to the nanowires. FMR was observed as an intensity reduction of the transmitted (S21) microwave signal at the appropriate DC field. As expected, the characteristic FMR behavior of Ni, Fe, and Co yielded six different trends of microwave absorption vs. DC field: three for parallel and three for perpendicular fields. In a simultaneous measurement of Co and Ni nanowires, distinct absorption peaks were evident, which means their signatures were distinguished from the mixture. Moreover, with this technique, nanowires coated with target cell-specific antibodies have potential to be successfully utilized to tag cells in drug delivery, hyperthermia, or cellular barcoding and manipulation.

TRACK 2
Nano/micro fluidics

Track Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*
Track Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

2-2
MOLECULAR DIAGNOSTICS USING NANO/MICRO FLUIDICS
Los Angeles, OMNI Hotel, Crocker room 3:30pm - 4:50pm

Session Organizer: **Joseph Liao**, *Stanford University, Palo Alto, CA, United States*
Session Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

Biosensor Applications for the Emerging Threat of Microbial Resistance

Keynote. NEMB2018-6287

Joseph Liao, *Stanford University, Palo Alto, CA, United States*

Rapid diagnosis of bacterial infections and timely initiation of appropriate treatment are paramount towards promoting optimal clinical outcomes and general public health. Bacterial pathogens that cause blood stream infections, surgical site infections, and urinary tract infections are highly adept in acquiring mechanisms of antimicrobial resistance. Widespread practice of empiric antibiotic usage has accelerated selection and dissemination of resistant pathogens. Conventional in vitro diagnostics for infectious diseases are time-consuming and require centralized laboratories, experienced personnel and bulky equipment. Advances in integrated biosensors, molecular probes, microfluidics, and single cell analysis have the potential to deliver point-of-care diagnostics that match or surpass conventional standards in regards to time, accuracy and cost. Using urinary tract infection, the most common community-acquired and healthcare-associated infection, as a model, we will review the current state of bacterial molecular diagnostics for pathogen identification and antimicrobial susceptibility testing and discuss the critical challenges in translation of these promising technologies from research laboratories to routine clinical application.

An Autonomous Pressure-Driven Siphon-Based Micropump for Long-Term Perfusion

Student Competition Presentation. NEMB2018-6244

Da Zhao, *University of California, Irvine, Irvine, CA, United States*, ***Xiaolin Wang***, *Shanghai Jiao Tong University, Shanghai, China*, ***Abraham Lee***, *University of California At Irvine, Irvine, CA, United States*

Autonomous and self-powered micropumps are in critical demand for versatile cell/tissue-based applications in microfluidic fields. The hydrostatic pressure-driven micropumps are widely used, but they cannot maintain steady and continuous flow for long periods of time. Here, we present a hydrostatic pressure-driven micropump with siphon-based autofill function, which can realize autonomous and continuous perfusion with well-controlled steady flow over an extended time.
The basic components in this micropump are medium storage container (MSC), 2 siphons, and microfluidic chip with inlet medium reservoir (IMR) and outlet medium reservoir (OMR). A tightly sealed conical tube as the MSC is fixed above the IMR. Two plastic tubings with different heights function as siphons to connect the MSC and IMR. To control the liquid level in the OMR, another tube was inserted at the bottom of the OMR to divert redundant medium into a waste container. Microfluidic chips with different microchannel designs can be integrated into this platform for versatile applications. During experiment, low siphon supplies medium to the IMR, and high siphon gets air into the MSC to balance its pressure. The medium will stop at the draining point of the high siphon. Therefore, a constant hydrostatic pressure drop between the IMR and OMR can be generated to supply the steady flow inside the microfluidic chip, which also enables the long-term perfusion with the siphon-based autofill function. We also improved our system with a 3D printed integration scheme to fix all the components in the right position, which kept the system stable during operation and transportation.

As a model application, a microvascular network formation model was established. The hydrostatic pressure drop was steadily maintained. Vascular network was developed through day 5. Then vascular network was lumenized and interconnected, and this could last for more than 14 days. Besides the advantage of steady flow, the enhanced micropump also enabled long-term perfusion for up to 5 days without the need to supplement medium to the MSC. This is 2 to 3-fold longer than our previous culture method, which needs medium change every other day.

In summary, we have developed an enhanced hydrostatic pressure-driven micropump for versatile microfluidic applications. The configuration of the entire system is simple and portable, and the related components can be easily acquired. With the siphon-based autofill function, the steady flow rate with precise control can be autonomously and continuously supplied for long terms.

Simple yet effective molecular concentration method using bidirectional flow in microfluidic platform

Student Competition Presentation. NEMB2018-6143

Sanghyun Lee, *Pohang University of Science and Technology (POSTECH), Pohang, Korea (Republic)*, ***Hojin Kim***, *RadianQbio, Seoul, Korea (Republic)*, ***Joonwon Kim***, *Pohang University of Science and Technology (POSTECH), Pohang, Korea (Republic)*

Recently, microparticle-incorporated microfluidic platforms have attracted great attention as a powerful tool for immunoassay due to their benefits such as small sample volume consumption, multiplexing capability. In order to conduct particle-based immunoassay, surface of particles should be functionalized (e.g., antibody conjugation) to capture molecules of interest (e.g., antigen) and then placed in a specific position for observation. Physical barriers (e.g., micropillars, weirs) or external forces (e.g., electric field, optical tweezer) are utilized to immobilize the surface-functionalized microparticles in microfluidic devices. Then presence of target molecules can be detected from the signal of the particle after the reactions between the immobilized particles and introduced samples. However, the main challenge in microscale reaction is that the laminar flow characteristic of microfluidics makes it difficult to achieve effective mixing and thus it requires time-consuming incubation to conduct assays in microscale. To enhance the mixing efficiency and molecular binding chance, local turbulent flow can be utilized for rapid reaction which can be caused by bidirectional flow pattern. In this situation, maintaining the particle position is necessary to conduct particle-based reaction. Simple physical barrier microstructures cannot hold the particle under the bidirectional flow. External force-assisted methods can hold the particle under the bidirectional flow, but complex experimental setup is required.
In this regard, we present an array format microfluidic device that enables effective molecular concentration on microparticles by robust holding of multiple microparticles against the bidirectional flow without the need of complicated setup. Each array element has the unique microstructure containing microparticle accommodation chamber and flexible thin membrane that can be deformed by the flow-induced shear stress. Microparticles can be trapped in front of the each array element and then enter the inside of chamber by flexible membrane deformation. The particles can be secured in the chamber against the bidirectional flow condition, thereby allowing effective molecular concentration with induced local turbulent mixing. For proof-of-concept, concentration and detection of small volume and low concentration biotin sample was demonstrated using an array of streptavidin-coated microparticles under periodic bidirectional flow condition.

A Microfluidic Device for Electrical Quantification of Surface Antigen Density via Magnetophoresis
Technical Presentation. NEMB2018-6270

Ozgun Civelekoglu, Ningquan Wang, Mert Boya, Tevhide Ozkaya-Ahmadov, Ruxiu Liu*, Georgia Institute of Technology, Atlanta, GA, United States*, **Fatih Sarioglu***, Georgia Tech, Atlanta, GA, United States*

Membrane antigens dictate biochemical interactions of cells, and their expression is of interest in clinical and biological research. Identification of the antigen type and quantification of its expression, especially at single cell level, are vital steps in a wide range of applications from medical diagnosis and prognosis to drug discovery. Cell surface expression can be measured using fluorescence-based flow cytometers. However, these instruments are expensive, bulky and also require a trained operator; hence, the availability of flow cytometers is restricted to centralized facilities. Therefore, a low-cost, portable alternative to fluorescent flow cytometers would greatly enhance their adoption, especially in resource-limited environments, where it can potentially be transformative in global health applications.
Here, we present an integrated microfluidic system to electrically profile the surface antigen density in a cell population. Our system combines magnetophoretic cell sorting with code-multiplexed Coulter counters (Microfluidic CODES). In operation, cells immunomagnetically labeled against a membrane antigen are deflected in the transverse direction based on their magnetic load (that is proportional to the surface expression level) from their otherwise straight course under an externally applied magnetic field. Deflected cells are collected in an array of discrete outlets, which are concurrently monitored by Microfluidic CODES sensors. Because each sensor is encoded with specially-designed orthogonal digital codes to generate signature electrical waveforms for a passing cell, all sensors can be read simultaneously from a single electrical output. Our device consists of three parts: a microfluidic layer fabricated from polydimethylsiloxane (PDMS) via soft-lithography, a glass substrate with electrical sensors fabricated using a lift-off process, and an on-chip permanent magnet. The magnet?s location is inscribed in the PDMS layer.
With our device, we analyzed the Epithelial Cell Adhesion Molecule (EpCAM) expression of MDA-MB-231 breast cancer cells. MDA-MB-231 cells were labeled with antibody-conjugated 1µm-diameter magnetic beads. Cells were pneumatically driven into the device at 50 mbar and the electrical signal generated by the sensor network was sampled into a computer. Following calibration of the device, signals were computationally analyzed to obtain a cell surface expression histogram. Comparison of our results with a conventional flow cytometer demonstrated successful characterization of the cell surface expression.
In summary, we present an integrated microfluidic device to electrically profile the surface antigen expression in a cell population. Our device can be considered as a portable, frugal, electronic alternative to the conventional fluorescence-based flow cytometers.

TRACK 7
Plenary Speakers

7-1
PLENARY SESSION I
Los Angeles, OMNI Hotel, Bunker Hill Room 5:00pm - 5:50pm

Session Organizer: **Bumsoo Han***, Purdue University, West Lafayette, IN, United States*

Quantum Biophotonic Electron Transfer and Its Applications in Medicine: Ultrafast Photonic PCR-based Precision Molecular Diagnostics System
Plenary. NEMB2018-6286

Luke Lee*, UC Berkeley, Berkeley, CA, United States*

In this talk, I will present quantum biological electron transfer and its applications in life sciences and medicine. First, I will introduce a quantum plasmonic nanoscope that allows non-invasive optical imaging of quantum biophotonic electron-transfer (QBET) dynamics in live cells. The quantum biological nanoscope is designed to capture the real-time QBET imaging of enzymes via Plasmon Resonance Energy Transfer (PRET) mechanism and quantized plasmon quenching dips in resonant Rayleigh scattering spectra.
Second, I will discuss ultrafast quantum photonic PCR-based precision molecular diagnostic systems. This system comprises three key elements: (1) ultrafast photonic amplifications of NA biomarkers; (2) signal amplifications of protein biomarkers; (3) a self-contained sample preparation for liquid biopsy on chip, which allows a sample-to-answer readout platform. If time permits, I will also present organoids on chip, or microphysiological analytics platforms (MAPs) as innovative solutions in systematic pathogenesis and personalized medicine. In particular, the real-time imaging of pathogenesis and evolution of mini-brains MAP with QBET, pancreatic islets MAP, and 3D kidney organoids MAP will be discussed along with the vision of personalized precision medicine.

Track 9
Posters and/or Student Poster Competition

Track Organizer: **Masa Rao***, University of California, Riverside, Riverside, CA, United States*
Track Co-Organizer: **Zhenpeng Qin***, Univ of Texas At Dallas, Richardson, TX, United States*

9-1
POSTER SESSION
Los Angeles, OMNI Hotel, Watercourt Room
6:00pm - 8:00pm

Session Organizer: **Masa Rao***, University of California, Riverside, Riverside, CA, United States*
Session Co-Organizer: **Zhenpeng Qin***, Univ of Texas At Dallas, Richardson, TX, United States*

Elastic Kelvin-Poisson-Poynting Solids Described Through Conjugate Scalar Stress/Strain Pairs Derived from a QR Factorization of F
Poster Presentation. NEMB2018-6104

Shahla Zamani Mehrian*, Texas A&M University, Bryan, TX, United States*

A kinematic description for the motion of a deformable body that was constructed out of a Gram-Schmidt factorization of the deformation gradient recently derived. Specifically, the metric tensor that associates with a convected coordinate system was quantified in terms of the physical attributes that arise from an upper-triangular decomposition of
the deformation gradient. It is within a rectangular, Cartesian, coordinate
system, created by this Gram-Schmidt factorization, that a frame of reference exists wherein physical components for convected vector and tensor
fields are quantified. In this paper the authors derive two viable sets of
thermodynamically admissible stress-strain pairs that are quantified in terms
of physical components from a convected stress and velocity gradient, with
elastic models being presented for both sets. The first model supports two
modes of deformation: elongation and shear. The second model supports
three modes of deformation: dilatation, squeeze and shear. These models
are distinguished by their pure- and simple-shear responses. These models
contain the coupling effects of Kelvin, Poisson and Poynting. Furthermore, we show that the Lodge-Meissner effect from rheology and
the Poynting effect from solid mechanics are the same physical phenomenon.

A Handheld Platform Based on Wash-Free Magnetic Bioassays for the Early Diagnosis of Influenza A Virus
Student Competition Presentation. NEMB2018-6120

Diqing Su, Kai Wu, Venkatramana D Krishna, Jianping Wang*, University of Minnesota, Minneapolis, MN, United States*
Early diagnosis of influenza A virus (IAV) is crucial for controlling the infection of possible influenza pandemic. Several kinds of nanotechnologies including silicon nanowires, carbon nanotubes, and gold nanoparticles have been developed to improve the efficiency and sensitivity of IAV detection. However, these methods often require complex instruments, which makes it difficult to realize onsite diagnosis.
Herein, we present a handheld system with wash-free magnetic bioassays to realize the diagnosis of IAV. Superparamagnetic nanoparticles are used as magnetic tags during the detection, which can attach to the target protein on the surface of a giant magnetoresistance (GMR) sensor.

The stray field from the magnetic nanoparticles will then be picked up by the sensor, with the magnetic signal proportional to the concentration of the target protein. By mixing the detection antibody, magnetic nanoparticles and the antigen all together at the same time without repeated washing procedures in the traditional bio-functionalization process, we managed to simplify the testing protocol with minimum sacrifice of device performance. The detection limit for IAV nucleoprotein is as low as 0.3 nM. Meanwhile, the validity of detecting unprocessed nasal swab samples from pigs has also been proved with comparable sensitivity to Enzyme linked immunosorbent assay (ELIZA). Furthermore, by integrating the wash-free bioassay with the handheld device, an accurate and efficient point-of-care platform is developed, which is capable of performing daily routine tests that can even be done at home by non-technicians.

Constructing a Fluorescence Lifetime Nanoprobe Library to Advance Lifetime-Based Multiplexing

Poster Presentation. NEMB2018-6122

Louis Mejia, Ashwin Kainkaryam, Rajesh Kota, Soo Song, Lauren Lastra, Enrico Gratton, Jered B. Haun*, University of California, Irvine, Irvine, CA, United States*

Cancer remains the second leading cause of death in the U.S. due to its complex and dynamic nature, particularly intra-tumoral cellular heterogeneity. Thus, key cell types must first be identified so that precisely targeted therapies can be employed. While fluorescent imaging remains the most common approach to assess molecular information, it is limited to 5-10 detection channels due to spectral overlap of fluorescent probes. Further increasing detection capacity would require an orthogonal means of resolving fluorescent probes. The excited state lifetime holds exciting potential to serve as this orthogonal metric, but the diversity of lifetimes currently available in off-the-shelf fluorescent probes is very limited. In this work, we advance the potential of lifetime-based multiplexing by developing a library of fluorescent nanoprobes with uniform and well-controlled fluorescence lifetime properties. Our unique strategy is to start with luminescent quantum dots, which display excited state lifetimes in the microsecond range. We then modulate lifetime by encapsulating quantum dots within silica nanoshells, along with quencher dyes, in a well-controlled and reliable manner. This would shorten the inherent lifetime, resulting in a functionally unique lifetime nanoprobe. Further modification to the nanoprobe exterior terminates with the addition of bioorthogonal click chemistry linkers. Our final antibody-targeted lifetime nanoprobes were imaged using fluorescence lifetime imaging microscopy and analyzed using the phasor method, both in free solution and after incubating with cancer cell lines. We have successfully manipulated the lifetime of a single quantum dot across the phasor plot by encapsulating within a silica nanoshell along with quencher dye. We are presently optimizing cell labeling and validating additional biomarker targets so that a full panel of lifetime nanoprobes can be simultaneously deployed for resolving molecular information using only lifetime information.

Signal-amplifying nanoparticle/hydrogel hybrid microstructure bioassay for metal-enhanced fluorescence detection of paraoxon

Poster Presentation. NEMB2018-6123

Minsu Kim, Ji Hong Min, Kanghee Cho, Hye Jin Hong, Gyeongju Kim, Won-Gun Koh*, Yonsei university, Seoul, Korea (Republic)*

Recently, the fluorescence detection method utilizing metal-enhanced fluorescence (MEF) has been widely studied in an effort to improve the detection sensitivity of protein-based bioassays. MEF is now a well-established technology, wherein the interactions of fluorophores with metallic nanoparticles results in fluorescence enhancement. In this study, as one solution for the problems associated with plate- and particle-based platforms, we developed a novel silver-based MEF biosensing platform that consisted of poly (ethylene glycol)(PEG) hydrogel microstructures entrapping silica-coated AgNPs (Ag@silica). Hydrogels are three-dimensional polymeric structures that absorb water or other biological fluids, and as it have a soft and hydrated nature, biomolecules is retained their activation. So, We took advantage of the MEF from Ag@SiO2 within the hydrogel microstructures to improve the performance of the fluorescence detection device.

Highly sensitive metal-enhanced fluorescence biosensor prepared on Ag@SiO2 decorated electrospun fibers

Poster Presentation. NEMB2018-6124

Byung Ju Yun, Jae Sang Lee, So Young Noh, Semin Kim, Hye Yeon Gong, Won-Gun Koh*, Yonsei university, Seoul, Korea (Republic)*

A new metal-enhanced fluorescence-based immunoassay platform was prepared on fibrous substrates. First, polycaprolactone (PCL) fibers were obtained via electrospinning process. PCL fibers were decorated with photoreduced silver nanoparticles and then, coated with silica, generating Ag@SiO2-PCL. The silica layer acted as a spacer between the silver nanoparticles and the fluorescent molecules to optimize the MEF effect. The fibrous structure of Ag@SiO2-PCL had higher protein loading capacity than conventional glass slides due to its large surface area, while the presence of silica-coated silver nanoparticles resulted in higher fluorescence intensity than in bare PCL fibers via the MEF effect. Both features of Ag@SiO2-PCL were combined to produce synergetic effects in improving the performance of fluorescence-based biosensing.

Antimicrobial Ag/a-C:H nanocomposite coated titanium substrates for implant applications

Poster Presentation. NEMB2018-6125

Monica Thukkaram, Pieter Cools, Rino Morent*, Ghent University, Ghent, Belgium*, ***Nathalie De Geyter****, Ghent University, Gent, Belgium*

Bacterial infections associated with titanium implants remain a common problem in the orthopedic field. To overcome this, antibacterial plasma polymer nanocomposites have been studied for years due to their antibacterial potency. Unfortunately, the application of these nanocomposites is often hindered by the fact that they are soft and not mechanically stable. Therefore, a hard plasma polymer layer is crucial that can withstand wear abrasion and at the same time shows antibacterial potency. In this study, a low-pressure plasma-based method was employed for the deposition of hard polymeric nanocomposite coatings containing Ag nanoparticles (AgNPs) on Ti substrates. This method uses a gas aggregation source (GAS) for the formation and deposition of Ag nanoparticles and combines it with plasma enhanced chemical vapor deposition of an amorphous hydrocarbon matrix (a-C:H) that is deposited in a mixture of Ar and n-hexane on substrates placed on a powered RF electrode. The matrix properties can be modified by adapting the applied RF power while the amount of incorporated Ag nanoparticles can be altered by the operational parameters of the GAS. The focus of this study is to deposit an a-C:H matrix containing Ag nanoparticles on Ti substrates and to optimize the working parameters to achieve a mechanically stable coating possessing anti-bacterial properties. Three different types of nanocomposite layers are studied: 1) nanocomposite films by simultaneous deposition of AgNPs and an a-C:H matrix 2) sandwich structures with base and top layers of a-C:H and an AgNP interlayer 3) quasi sandwich films with a base layer of a-C:H and a second layer of simultaneous deposition of AgNPs and an a-C:H matrix.

UV-Vis spectroscopy was employed to characterize the Ag nanoparticle deposition efficiency at different operational parameters of the GAS. The morphology and chemical composition of different nanocomposite films were studied with SEM-EDS and XPS. Additionally, the antibacterial performance and the Ag ion release rate of the differently prepared samples were investigated. In this way, optimization of the coating deposition process resulting into hard coatings with a prolonged antibacterial efficiency will be achieved.

In vitro study of transvascular transport of nanostructures using a 3D printed microfluidic platform

Poster Presentation. NEMB2018-6126

Ronghui Ma, Liang Zhu, Marie-Christine Daniel, Myo Min Zaw, Jordan Bendler, Chanda Lowrance, Qimei Gu, Arun Saha-Ray*, University of Maryland Baltimore County, Baltimore, MD, United States*

Nanostructures have been developed to target specific tumor cells or diseased tissue to increase the drug concentration in tumors while minimizing systemic toxicities. Existing studies have shown that nanorods are more likely to deposit on the capillary wall than their spherical-shaped counterparts. However, whether these shapes could ultimately improve targeting efficiency remains unclear because the elongated shapes might hinder their penetration through the fenestra of the leaky tumor vasculature. Unfortunately, characterizing nanostructure interactions with the tumor vasculature in vivo is difficult due to the small length scale of the nanostructures and lack of pre-clinical/animal experimental control.

In this study, we develop a microfluidic platform to mimic nanoparticle transport through tumor vasculature. Unlike traditional method for fabricating microfluidic devices, 3D printed parts serve as master molds to create the designed patterns on polydimethylsiloxane (PDMS) parts.

The platform consists of a capillary channel, a chamber, and a permeable membrane. Nanoparticles are infused into the capillary channel to penetrate the membrane and to be deposited in the chamber, driven by a positive pressure difference between the channel and the chamber. The nanoparticle concentration in the chamber is measured using a fluorescence spectrophotometer to evaluate the rate of extravasation. The microchannels are 500 microns in width and 200 microns in depth. The membrane pore size is one micron. The pressure difference between the capillary and the chamber can be adjusted to mimic the effect of elevated interstitial pressure in tumors in vivo. The microfluidic platforms are generated using soft lithography method.
The microfluidic platform is used to evaluate how the nanostructures of different shapes respond to changes of interstitial pressure. Transport of nanoparticle with nominal diameters of 20 nm and nanorods with diameter of 20 nm and an aspect ratio of 2 are tested under three pressure differences between capillary and the chamber, which are 20, 30 and 40 mmH2O. The transvascular transport rate of the nanoparticles would help understand the transport behavior of nanoparticles in the human body and be used to optimize nanoparticle size and shape towards improving delivery efficacy. This study has demonstrated that 3D printing systems have the potential to replace the complex and time-consuming microfabrication steps in a cleanroom, thus, eliminating the dependence on the institutional infrastructure. Use of the 3D printing system also reduces need for extensive training, protracted fabrication time, and expensive operational costs associated with traditional prototyping methods, enabling agile iterative design and optimization.

Enhanced Alignment of the Neural Stem Cells on the Touch-Spun Nanofibrous Scaffolds

Poster Presentation. NEMB2018-6131

***Se Jun Lee**, George Washington University, Washington, DC, United States*, ***Darya Asheghali, Sergiy Minko**, University of Georgia, Athens, GA, United States*, ***Lijie Zhang**, George Washington University, Washington, DC, United States*

Electrospinning has been examined in numerous studies for the fabrication of biomimetic nano/microfibrous scaffolds for nerve regeneration. However, this conventional method of processing fibers is extremely dependent on the dielectric properties of the polymer solution. Moreover, the applied high-voltage in electrospinning has negative effects on the loaded biomolecules. In this study, we utilized a novel touch-spinning technique to create polymer nanofibers without using high-voltage electric field for neural regeneration. The primary objectives of the study are to (1) evaluate the feasibility of utilizing a touchspinning set-up to create a highly aligned and nanoscale scaffold, and to (2) examine the proliferative capability and differentiation potential of neural stem cells (NSC) seeded in the resultant scaffold in vitro.

This touchspinning system consists of a simple controllable setup for drawing single filament nanofibers from polymer solutions using a rotating rod. A highly aligned touchspun polycaparolactone (PCL) nanofibers with extremely high crystallinity degree and improved mechanical properties were fabricated. A conventional electrospun scaffold as a control was also fabricated using a drum rotator. The scaffold morphology and diameter were characterized using a scanning electron microscope. The crystal structure of PCL nanofibers prepared by two techniques was confirmed by X-ray diffraction (XRD) analysis. The uniaxial mechanical properties were examined. The electrospun and touchspun scaffolds were seeded with NE-4C neuroepithelial cells (NSCs) for biocompatibility evaluation. The highly aligned electrospun and touchspun fibers had fiber diameters of approximately 670 and 700 nm respectively.
XRD analysis revealed that peak positions for both electrospun and touchspun PCL fibers were essentially identical, suggesting no change in crystal structure by fabrication techniques. However, the degree of crystallinity of the touchspun fibers was greater than that of electrospun fibers at various spinning rates. Also, the Young?s modulus values of the touchspun fibers at various spinning rates were much higher (>>600%) than those of electrospun fibers. NSCs exhibited an elongated neurite growth along the touchspun PCL nanofibers at varying spinning rates, whereas, they tended to aggregate on the entangled electrospun PCL nanofibers. As the spinning rate of the touchspun nanofibers increased, the percentage of neuronal cells generated from NSCs increased. These results have shown the feasibility and promise of using the touchspinning technique to fabricate fibrous scaffolds for neural tissue engineering applications.

Aging Immunity: Monocyte Derived Dendritic Cell?s Metabolic Shift associated with Human Aging

Student Competition Presentation. NEMB2018-6140

***Albert Liu, Silin Cai, Anshu Agrawal, Michelle Digman**, University of California, Irvine, Irvine, CA, United States*, ***Abraham Lee**, University of California At Irvine, Irvine, CA, United States*

Human aging is often linked to the gradual decline of the immune system. This age-related decline of the immune system, or immunosenescence, is often attributed to the increased frequency of elder morbidity and mortality. One prominent immunosenescence feature is that of a low grade chronic inflammation. Dendritic cells (DC) play a major role in adaptive immunity that governs inflammation by presenting pathogenic antigens at T-Cells to initiating immune response. Once activated, dendritic cells undergo physiological transformation and express a host of costimulatory and proinflammatory molecules. This transformation requires a shift in metabolic demand in order to meet the bioenergetic and biosynthetic needs of activated dendritic cells. We hypothesized that aging initiates excessive dendritic cell activation which could in turn triggers chronic inflammation observed in elderly subjects. Through studying cellular metabolic markers from microfluidic aided fluorescence lifetime Imaging microscopy (FLIM) and flow cytometry, we report the preliminary results on the metabolic effect of aging on dendritic cells.

Dropwise microstructure of a thermally responsive hydrogel by drop-on-demand printing for advanced manufacturing

Poster Presentation. NEMB2018-6147

***Yoon-Jae Moon, Jun Young Hwang**, KITECH, Ansan, Korea (Republic)*, ***Cih Cheng, George Chiu, Bumsoo Han**, Purdue University, West Lafayette, IN, United States*

Hydrogel-based soft materials are widely used in various applications including healthcare, food, pharmaceutical, and cosmetic products. In addition, recent developments of polymer sciences enable a wide variety of novel hydrogel-based soft materials, whose properties can be designed and tailored for new advanced applications including tissue engineering, controlled drug delivery, stretchable and wearable electronics, and energy storage and conversion. To enable these new products as well as to improve current ones, it is crucial for manufacturing equipment and process to have the capability of integrating these novel materials into three-dimensional (3D) parts with prescribed spatially varying functional properties. However, hydrogel-based materials are very delicate and fragile to handle and conventional manufacturing methods are not adequate to produce their functional parts. In this context, drop-on-demand (DOD) printing technologies shows great potential to address this manufacturing challenge and will enable additive manufacturing of advanced soft materials by depositing hydrogel drops with desired functional properties at desired positions with appropriate timing between adjacent drops. However, it is currently extremely difficult to design DOD printing processes for hydrogel materials due to limited mechanistic understanding of the behaviors of printed hydrogel drops during and after deposition, which will eventually determine the functional properties of the printed products. In the present study, we performed both experimental and computational study to establish a mechanistic understanding of the behaviors of hydrogel ink drops during DOD printing processes for manufacturing of hydrogel products. Specifically, we characterized the gelation of printed drops and their concurrent and/or subsequent dehydration phenomena. This research is based on a hypothesis that complex interaction between polymer matrix and interstitial water occurs during this dropwise gelation-dehydration and the result of this interaction will determine the microstructural characteristics of polymers at intra-, inter-drop and inter-layer scales, ultimately porosity of the hydrogel printed.

3D Printed Scaffold With Hierarchical Biomimetic Structure For Osteochondral Regeneration

Poster Presentation. NEMB2018-6150

***Xuan Zhou**, The George Washington University, Washington, DC, United States*, ***Timothy Esworthy**, George Washington University, Washington, DC, United States*, ***Raj Rao**, the george washington university, WASHINGTON, DC, United States*, ***Lijie Zhang**, George Washington University, Washington, DC, United States*

Osteochondral defects from disease or physical trauma are a common and disabling health concern. The concept of articular cartilage repair is attractive due to the inherently weak regenerative capacity of osteochondral tissue. Currently, surgical approaches for osteochondral lesions include replacement with autograft, allograft, or xenograft implantation. However, due to an array of physiological and economical challenges associated with these surgical interventions, they are still not an entirely satisfactory set of therapeutic options.
The emerging technology of 3D bioprinting has shown great promise in fabricating customizable tissue constructs. In this study, a biomimetic scaffold with biphasic hierarchical structure was fabricated to promote osteochondral regeneration using our custom-designed stereolithography (SL)-based printer. Specifically, gelatin methacrylate (GelMA) and polyethylene (glycol) diacrylate (PEGDA) were utilized as the printing ink (GelMA-PEGDA).

For the subchondral bone layer, nano-hydroxyapatite was added into GelMA-PEGDA. For the cartilage layer, TGF-?1 loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles prepared by a co-axial electrospraying method, were notably well incorporated into our GelMA-PEGDA ink. Finally, our fully assembled biomimetic, 3D printed biphasic scaffold with distributed TGF-?1 and nHA (GelMA-PEGDA-nHA/TGF-?1 PLGA NPs) was seeded with human bone marrow mesenchymal stem cell (hMSCs) in order to assess their subsequent osteochondral differentiation. The results showed that the TGF-?1 loaded nanoparticles with 120 nm particle sizes were prepared for a sustained growth factor release. In addition, uniform pores and channels were arranged in an orderly fashion within the printed constructs. The gene expressions associated with both osteogenesis (Collagen I, Osteocalcin, Osteopontin, Alkaline phosphatase, and Runt-related transcription factor 2) and chondrogenesis (Collagen II?1, Sox-9, and Aggrecan) were greatly promoted within our constructs, as evidenced by qRT-PCR. Moreover, histological assessment demonstrated that the biphasic scaffold promoted osteogenic and chondrogenic differentiation of the hMSCs. This study demonstrated that 3D printed osteochondral scaffolds with biphasic structures are promising for osteochondral regeneration applications.

Cortex Wide, Multi-Modal Neural Interfacing via Transparent Polymer Skulls

Student Competition Presentation. NEMB2018-6152

Leila, L. Ghanbari, Russell E., R.E. Carter, Mathew, M. Rynes, Judith, J. Dominguez, Jay J, J.J Hu, Nahom, N. Mossazghi, Michael, M. Laroque, Timothy J., T.J. Ebner, Suhasa B., S.B. Kodandaramaiah*, University of Minnesota, Minneapolis, MN, Minneapolis, MN, United States*

The brain mediates our interaction with the external world by performing complex computations undertaken by highly interconnected regions spread across several centimeters. To understand how computations occurring globally mediate behavior, we need tools to measure and manipulate the activities of these widespread brain regions at the single cell resolution, and at multiple timescales. Currently, appropriate tools to access large brain regions while simultaneously sampling information at high rates are not available. The ability to perform such multi-scale imaging in the context of neural perturbation of localized regions of the brain would be very powerful. To this end, we have developed ?See-Shells?, digitally generated transparent polymer skulls, that enable wide-field sub-cellular resolution optical access to the whole dorsal cortex in mice.

We used a motorized stereotax to map the skull surface of a 9-week old C57/BL6 mouse at 85 points to generate a 3D point cloud. We used this point cloud to interpolate a general 3D surface that accurately mimicked the morphology of the skull and subsequently used the interpolated surface as a template to digitally design skull replacements using computer aided design (CAD, SolidWorks) software. The See-Shells consist of a 3D printed PMMA frame bonded to a transparent, thin and flexible polymer, Polyethylene terephthalate (PET) using an adhesive epoxy. See-Shells were implanted on 16 C57/BL6 mice, 2 Thy1-YFp mice, and 27 Thy1-GCaMP6f mice by adapting previous window implantation protocols.

See-Shells were chronically implanted and allowed optical access for over 100 days. We demonstrate the ability to image sub-cellular structures such as dendrites and dendritic spines at depth in vivo using two-photon (2P) microscopy. We also performed wide-field imaging of mesoscale activity in awake head-fixed animals, as well as imaged the activity of individual neurons (often hundreds) in localized cortical regions spread across several millimeters using 2P microscopy. Perforating the PET allowed us to introduce probes for intra-cortical stimulation of the motor cortex while performing cortex wide imaging. We observed that localized stimulation of the motor cortex causes global activation of the whole cortex in both anesthetized and awake animals. Thus, See-Shells enable us to chronically interface with the cortex at high spatial and temporal resolution, at both mesoscale and cellular levels, in the awake animal.

Rapid Microbial Screening Using Cell Nanocoating

Poster Presentation. NEMB2018-6158

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Nanocoating of single microbial cells with gold nanostructures can confer optical, electrical, thermal, and mechanical properties to microorganisms, thus enabling new avenues for their control, study, application and detection. By taking advantage of surface functional groups densely present in the microbial outer layers, cell nanocoating with gold nanoparticles can be achieved within seconds using pre-treatment processes. These target functional groups include free thiol groups yielded from chemical reduction of disulfide- bond-containing (Dsbc) proteins and free amine groups formed from deacetylation of chitin. Upon activation, these markers and their subsequent interaction with gold nanoparticles allow specific microbial screening and quantification of bacteria and fungi within 5 and 30 min, respectively. Both plasmonic methods and fluorescence methods have been employed using this technique offering limits of detection below 35 cfu/mL for E. coli bacteria and 1500 cfu/mL for M. circinelloides fungi.

Anti-Proliferation of Breast Cancer Cells Regulated by DNA Walkers

Poster Presentation. NEMB2018-6168

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DNA walkers are a class of synthetic molecular motors that can move processively along prescribed pathways. Typically, a single-stranded DNA or multiple strands form a walker system with a series of anchor strands on a track template due to a free energy gradient created by DNA strand displacement, restriction enzymes or DNAzymes. While various DNA walking mechanisms have been proposed, research on their applications still remain limited. In this work, we introduce a DNAzyme-based walker system as a controlled oligonucleotide drug AS1411 release platform for breast cancer treatment. AS1411 is one of the G-rich oligonucleotides (GROs), which is an anti-proliferative drug toward multiple cancer cell lines at relative low concentrations.

As a walker moves along its carbon nanotube track, AS1411 strands are released from fuel strands. The release rate and amount of anti-cancer oligonucleotides can be controlled by density of fuel strands and walking speed (including ion concentration, type of DNAzyme and pH). With the walker system embedded within the collagen extracellular matrix (ECM) and breast cancer cells MCF-7 cultured on the top of ECM, AS1411 will gradually be release into ECM and diffused and absorbed by MCF-7. After 96-hour culturing in this condition, cancer cell viability is only ~60% compared to the cell culturing without DNA walker system embedded.

In summary, a DNA-walker-mediated platform that inhibits cancer cell growth in situ is created. Given the robustness of the release platform, our walker system may be extended for treatment of other cancer cell lines with appropriate drugs. Finally, we envision that the highly precise reaction pathways of the walker system could be exploited for additional regulating mechanisms in response to, for example, external photo-irradiation or environmental changes by sequence designs with functional moieties, forming a unique powerful molecular regulating system.

Feasibility of Visualization and Analyses of Deposition of a Newly Developed Dendritic Ligand-Coated Gold Nanoparticles in PC3 Tumors Using MicroCT Scan

Student Competition Presentation. NEMB2018-6181

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We developed 20 nm diameter gold nanoparticles conjugated with a carboxylate-terminated polypropyleneimine (PPI) dendron via ligand exchange reactions. Its structure, when demonstrated stable, can be used in the future to attach active targeting moiety such as recombinant monoclonal antibody 1C1 on the nanoparticle surface to improve nanoparticle uptake into cancer cells. Although it is known that only a portion of the drug carrying nanoparticles injected to the vein is eventually deposited in the targeted tumor, in this preliminary study we test the extreme situation to evaluate whether microCT scan is capable of distinguishing nanoparticles from the tumor tissue, assuming all the nanoparticles are deposited in the tumor. Two concentrations of the nanoparticles (3.2 mgAu/mL and 10 mg/Au/mL) were prepared, and the concentrations were confirmed by absorption spectroscopy.

PC3 xenograft tumors (10 mm in diameter) were implanted in 8 Balb/c Nu/Nu male mice. The tumors are randomized into three groups: 1) control group without nanofluid injection; 2) injection of 0.2 cc low concentrated nanofluid; and 3) injection of 0.2 cc highly concentrated nanofluid. The mouse was anesthetized by sodium pentobarbital (40 mg/kg, i.p.) before the nanofluid was injected to the tumor center. Later the mouse was euthanized by sodium pentobarbital overdose (160 mg/kg, i.p.). The tumor was then resected and scanned by microCT (Skyscan 1172, Microphotonics, PA).

MicroCT scan of each tumor after reconstruction resulted in a series of individual grayscale images with the intensities ranging from 0 being black to 255 being white. MicroCT images of tumors with nanofluid injection show a clear white cloud region correlated to the presence of nanoparticles.

The average grayscale value of the tumors in the control group is 43 and is relatively uniform over the entire tumor. With the injection of the low concentrated nanofluid (3.2 mgAu/mL), the average grayscale value increases 112% to 91.4, and it further increases to an average grayscale value of 121 in the tumors injected with the highly concentrated nanofluid (10 mgAu/mL). The spreading of the nanoparticles from the injection site is also evaluated using the full-width-at-half-maximum (FWHM). The FWHM in the tumor group with low concentration nanofluid injection is 1.3 mm, while nanoparticle spreading to the tumor periphery is evident in the tumor group with the high concentration nanofluid injection, resulting in an FWHM equal to 6.8 mm. In conclusion, we demonstrated that the microCT is capable of visualizing the developed gold nanoparticles in PC3 tumors.

Local Invasion of Pancreatic Cancer Cells Through a Periductal CAF Layer

Student Competition Presentation. NEMB2018-6184

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Cancer associated fibroblasts (CAF) have been known to promote the progression of pancreatic ductal adenocarcinoma (PDAC). However, several recent studies have reported that CAFs have anti-cancer roles by suppressing the growth and invasion of cancer cells. We hypothesize that these contracting roles are caused by the two different sub-populations of CAFs, interstitial and periductal, distributed within PDAC tumors. In order to test this hypothesis, a microfluidic tumor platform has been developed in which a three-dimensional channel is created within a collagen matrix, then cells are seeded along the wall of the channel to mimic an epithelial duct of the pancreas. This configuration allows for the seeding of CAFs within the collagen matrix to mimic the CAFs that are present in the surrounding stroma tissue in vivo, interstitial CAFs, and also allows for CAFs to be aligned along the duct of epithelial cancer cells, periductal CAFs. In this tumor platform, murine CAFs are first seeded around the duct to create an outer later, then murine pancreatic cancer cells (KPC-2), derived from PDAC tumors of genetically engineered mouse models, are seeded on top of the CAF layer to create a bilayer duct of CAFs surrounding cancer cells within a type I collagen matrix. Using this platform, local invasion of cancer cells is visualized as they penetrate through the surrounding CAF layer. The results suggest that CAFs may enhance the epithelial-mesenchymal-transition (EMT) and local invasion of cancer cells via biochemical interactions, but the physical presence of CAFs also hinders the invasion of cancer cells. The net impact of CAFs is thought to be determined by the balance of these periductal CAFs and the interstitial CAFs.

The Effect of Static Pre-stretch on Bladder Smooth Muscle Cells

Poster Presentation. NEMB2018-6189

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Neurogenic bladder, is a term used to characterize many urinary tract dysfunctions arising from the loss of control by the brain due to spinal cord injury (SCI), or other nerve-related problems. Some of the pathologies that may be complicated by neurogenic bladder dysfunction include multiple sclerosis, Parkinson?s disease, spina bi?da, and diabetes mellitus. The loss of neurological connection with the bladder cause a decrease or loss of sensation of fullness. In turn leads to increase in urine volume stored during ?lling (increased stretch/stress within the wall). This triggers remodeling of the extracellular matrix (ECM) due to this mechanical cue. In response, the neurogenic bladder shows hypertrophy of the smooth muscle cells, increasing elastin synthesis while decreasing collagen production. A neurogenic bladder has problems voiding all the urine in the bladder which commonly results in urinary tract infection and other disorders. Two diseases of interest in this proposal are spina bifida and diabetes mellitus. They have the similarity that elevated mast cells and the host defense peptide, LL-37, occur leading to bladder inflammation.
Previously, mesenchymal stem cells were cultured on a stretch device and found to induce cell differentiation and anisotropy. The project will investigate how the urinary bladder smooth muscle cells (SMCs) are affected by mechanical stimuli (stretch and substrate stiffness), what induces the SMCs to switch phenotypes from contractile to synthetic, and what products are produced by the SMCs that alters the ECM. We hypothesize that if bladder smooth muscle cells are subjected to a static chronic prestretch they will have elevated mast cells and levels of LL-37. The aim of this project is to study the effect of prestretched vs. unstretched surfaces on the elastogenesis of bladder smooth muscle cells.

Studies suggest collagen provides tensile strength, whereas elastin enhances tissue compliance. It is hypothesized that diabetes mellitus mediates the hypotrophy of the bladder through changes in gene expression of collagen and elastin. We will design experiments with the stretch device previously used in this lab, to determine whether (1) stretch / sti?ness or (2) cytokines (produced by SMCs) promotes changes in (i) gene and protein expressions of elastin, and collagen, and (ii) their phenotype (i.e., contractile vs synthetic) by analyzing the expression of h-caldesmon and alpha smooth muscle actin (??SMA). These experiments may help elucidate mechanisms associated with bladder dysfunctions and diseases such as diabetes mellitus and spina bifida.

Physical limits on chemotactic performance of cancer cells

Student Competition Presentation. NEMB2018-6195

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Chemotaxis occurs in many biological processes including cancer metastasis. In metastasis, tumor cell invasion to and migration through the surrounding extra-cellular environment are critical steps. In these steps, chemical signals are thought to play crucial roles by guiding the direction and enhancing the motility of the cells. However, it is still elusive how cancer cells sense and response to the signals. Specifically, it is poorly understood how the accuracy and persistence of cell directional motion are affected by the external cues.
In the present study, we focus on chemotactic performance of the cancer cells to identify physical constraints on sensing and responding capability of the cells theoretically and experimentally. Since the cells sense the external cue based on the diffusion, physics of diffusion directly results in the inherent limits on sensing capability of the cell. Based on the physics, we examine the physical limits on the performance by varying the chemical concentration gradients. The migratory behaviors are quantified with accuracy, persistence, and speed to elucidate the relation between the chemical concentration gradient and the chemotactic performance.
To do so, we perform chemotaxis assay using micro-fluidic channel device including human breast cancer cells, MDA-MB-231, embedded in 3D collagen matrix. The cells are exposed to transforming growth factor-beta1 (TGF-beta1) concentration gradient based on the principle of diffusion. In addition, we propose a theoretical model to predict the cell migratory behaviors using a biased persistent random walk. In both experimental and theoretical results, the accuracy of the directed movement is significantly promoted by increasing gradient of the chemical concentration. However, the accuracy is saturated at some point in the higher gradient. Unlike the accuracy, persistence is not affected by the varied concentration gradient. Subsequently, the results are projected to theoretical bounds on chemotactic performance based on the biased persistent random walk model. Using the theoretical approach, we show the physical constraints on chemotactic performances. This study will help to examine how the cells sense and response in the complex extracellular environment.

Biomimetic, 3D hydrogels to investigate effects of microenvironment biophysical properties on patient-derived glioblastoma (GBM) and endothelial cells (ECs)

Poster Presentation. NEMB2018-6196

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Introduction: This study investigated how the mechanical microenvironment of glioblastoma (GBM) tumors may affect morphology and phenotype of patient-derived GBM and brain endothelial cells (ECs) ? both critical components in the perivascular invasive niche.
Materials and Methods: Hydrogels were fabricated from thiolated hyaluronic acid (HA-SH) (0.5 w/v%) and 4-arm PEG-SH (1.5 w/v%), 8-arm PEG-norbornene (1.125 w/v%). Gelation occurred upon exposure to UV light (365 nm, 3-5.75 mw/cm2) for 15 s in the presence of a cytocompatible photoinitiator LAP (Lithium Pehnyl (2, 4, 6-trimethylbenzoyl) phosphinate, 0.025 w/v%). Patient-derived gliomaspheres or single dissociated ECs were mixed with hydrogel precursors prior to gelation. Phase contrast images were acquired every 3 days to monitor cell migration. After 9 days, 3D cultures were fixed, and cells visualized with CellMaskTM Green (ThermoFisher) and Hoescht (nuclei). Cell survival following encapsulation was evaluated using a Live/Dead Assay (Life Technologies). A Leica LSP5 confocal microscope was used to image 3D cultures. Storage moduli (G?) of hydrogels were measured using shear rheometer (TA DHR-2) with an 8-mm flat plate geometry.

Results and Discussion: Hydrogel stiffness (G?) was controlled by varying UV intensity to achieve a range of 150?1500 Pa, which are representative of the normal brain and tumor microenvironments, respectively. Gliomaspheres and ECs cultured showed comparable survival 7 days post-encapsulation in both soft and stiff gels. Gliomaspheres cultured in stiff hydrogels remained did not migrate away from spheroids, while cells encapsulated in soft hydrogels exhibited robust migration.
Our previous results showed that ECs residing in GBM perivasculature differentially express high amount of integrin-binding sialoprotein (IBSP). Survival of ECs in hydrogels baring different biophysical properties is an appropriate platform to study the effect of stiffness on ECs protein expression.
Conclusion: Patient-derived GBM and ECs were successfully cultured in 3D HA hydrogels mimicking biophysical properties of brain or GBM tumor tissue. GBM cells cultured in stiffer environments were unable to migrate, but upon culture in soft environments were found to migrate up to 200 μm away from seeded spheroids within 9 days of cultures.

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Spectral Imaging of Adipose Derived Adult Stem Cells

Poster Presentation. NEMB2018-6198

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Adipose-derived mesenchymal stem cells have the ability to differentiate into adipocytes, osteocytes, and chondrocytes which in turn can be developed into adipose tissues, cartilages, and bones. This regeneration capability has fueled increase in stem-cell research; and the need to develop state-of-art imaging modalities and analysis protocol for enabling characterization of the differentiation process efficiently, economically, and non-invasively. Authors have explored novel label-free imaging approach to study ASCs stimulated to differentiate into osteocytes. In this novel investigation we utilized transmitted dark field imaging technique to locate single as well as multiple osteoblasts a drop coated on the glass substrate. After recording optical image, we employed a hyperspectral spectroscopy technique within Vis- NIR spectrum (400-900 nm) at the same field of view to collect spectral response of the biological specimen. Response is stored in the three dimensional data-cube form with two spatial dimensions and one spectral dimension. No special tagging or staining of the ASCs and derived osteoblasts has been done, as required in traditional microscopy techniques. Sub-cellular heterogeneities present in the control ASCs and differentiating ASCs diffract incident light at multiple angles and hence scattering response received after transmission. To obtain insight of single molecule-level mineral deposits, proteins, fats, and other biological mono-constituents, we extract lipid information from matrix-assisted laser deposition/ionization spectrometry of control and differentiated stem-cells. Spectra from the known constituents are matched with in vitro stem cells via spectral angle mapping algorithms. . Optical images are investigated using template-match and edge-detection algorithms to provide secondary validation to the hyper spectral imaging results.

Selective Photo-Inactivation of Proteins in Live Cells by Molecular Hyperthermia

Poster Presentation. NEMB2018-6204

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Spatiotemporal manipulation of proteins has significant impact from treating cancer to chronic pain. For example, protease-activated receptors (PARs) belong to G-protein coupled receptors, which can be activated irreversibly by proteolytic cleavage of the N terminus. PARs are involved in cardiovascular disease, cancer and inflammations. Protease-activated receptor 2 (PAR2) is one of four PARs that can lead to chronic pain. Precise control of the PAR2 activity will bring promising opportunities in understanding and treating these diseases. However, the discovery of small molecules antagonists with high selectivity and potency is challenging.
Here we experimentally demonstrate that nanosecond pulsed laser heating of gold nanoparticles (GNP) leads to an ultrahigh and ultrashort temperature increase, coined as ?molecular hyperthermia?, which causes selective unfolding and inactivation of proteins adjacent to the GNP.
Firstly, we demonstrate that molecular hyperthermia leads to precise protein inactivation when targeted by GNPs. Here we conjugated an enzyme (alpha-chymotrypsin) to GNP (d = 5, 15, 30 nm) with a polyethylene glycol (PEG) spacer. Molecular hyperthermia is done by irradiating GNP with a nanosecond pulse laser at 532 nm (Quantel USA) and the enzyme activity was verified by a colorimetric enzyme assay. The experiment shows that the enzyme activity is dependent on laser energy, GNP size, spacer length and laser pulse number. When the enzyme is not attached to GNP, no inactivation was observed, suggesting a highly selective and localized effect. Further analysis of protein inactivation kinetics indicates a significant departure from Arrhenius kinetics at higher temperatures (>> 373K) during molecular hyperthermia.
Next, we demonstrate that molecular hyperthermia can be used to inactivate PAR2 on live cells without causing cell injury. An anti-human PAR2 antibody (MAB3949, R&D systems, USA) is firstly labeled on GNP (d = 45 nm). Then live HEK 293 cells are incubated with GNP solution for 30 mins to allow GNP target on PAR2 and are irradiated by nanosecond laser pulses to inactivate PAR2. The PAR2 activity is confirmed by checking endoplasmic reticulum calcium release modulated by PAR2 activation. The results shows that molecular hyperthermia leads to ~30% decrease in PAR2 activity, while no significant change was observed in control groups.
In summary, this study shows the molecular hyperthermia can selectively target and manipulate protein of interest in situ. Molecular hyperthermia is a novel tool for nanomedicine in biology as well as a potential therapeutic approach for disease treatment without genetic modification.
Authors acknowledge the grant support from NSF and UTDallas.

Enhanced Effect of Magnetic Nanoparticles on Acoustic Attenuation Coefficient of Tissue Mimicking Material during HIFU Ablation: A Comparison of Numerical and In Vitro Results

Student Competition Presentation. NEMB2018-6205

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Introduction:
High Intensity Focused Ultrasound (HIFU) is a hyperthermia therapy where tumors are ablated by means of thermal energy generated from attenuation of acoustic waves. Consequently, collateral damage may also occur to the surrounding tissues. Infusion of magnetic nanoparticles (mNPs) into tissues is proven to provide enhanced temperature rise during HIFU sonication (Deverakonda et al., PLOS ONE, 12(4): p. e0175093, 2017). Therefore, HIFU ablation of tumors in presence of mNPs can be achieved at lower powers, leading to minimal collateral damage to normal surrounding tissues. Hence it is important to assess the influence of infused mNP concentration on tissue ablation procedure. The objective of this study is to determine attenuation coefficient (a) of tissue phantoms infused with different physiologically acceptable mNP concentrations.
Method:
HIFU experiments and computations were performed at input powers of 10, 15 and 20 W to obtain focal temperature rises in three tissue phantoms (control [0%w/v], lower [0.047%w/v] and higher [0.2%w/v] concentration). Experimental setup includes HIFU transducer, tissue mimicking material and thermocouples (TCs). To avoid direct sonication of TCs that involve viscous heating-artifacts, the temperature rise was derived from exponential integral function from off-focal temperature measurements (Dillon et al., Phys Med Biol, 57(14): p. 4527-44, 2012). A finite-difference method (HIFU Simulator) was used for determining focal temperature which was compared with experimental data. An ?a? of 45 dB/m for control phantom was used as input for computation. For the phantoms containing mNPs, the ?a? was obtained from the computational model through back-calculation. The ?a? for each mNP infused tissue phantom was determined when computed temperature rise agreed with experimental value within 0.5%. This procedure was implemented for all power levels to check for consistency in ?a?. Subsequently, a correlation between ?a? and mNP concentrations was obtained.
Results:
A linear trend was observed between the ?a? and mNP concentration ($R2 = 0.99$). The ?a? of tissue phantom increased by 0.44 times and was statistically significant when control and higher concentration were compared ($p<0.05$).
Conclusion:
Infusion of mNPs in tissues can provide increased ?a? leading to enhanced temperature rise during HIFU sonication.

Optical opening of blood-brain barrier for macromolecules penetration by plasmonic nanobubble

Student Competition Presentation. NEMB2018-6209

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Brain tumors are known to be lethal, with a median survival of 14.6 months for glioblastoma multiforme. A major and unique obstacle for brain tumor drug delivery is the presence of blood-brain barrier. The blood brain barrier is a sophisticated structure that gives an optimal environment for brain function but also severely limits the penetration of anti-cancer drugs. The goal of our project is to develop a novel approach to optically open the blood-brain barrier thus allowing the access of a wide range of therapeutic drugs to brain tumor cells. Specifically, we designed and synthesized plasmonic nanomaterials to target the tight junction proteins, a critical component of the blood-brain barrier. By using picosecond pulsed laser, we generated plasmonic nanobubbles by activating targeted plasmonic nanomaterials. These nanobubbles then acted as ?nano-sonicators? to locally disrupt the tight junction thus temporarily compromising the blood-brain barrier. We tested our hypothesis both in vitro using a cell monolayer model and in vivo. Success of this work will significantly advance the field of brain tumor drug delivery. Specifically, the optically triggered blood-brain barrier opening will allow the use of more effective chemotherapy drugs from a large pool of anti-cancer drugs, previously unavailable due to the blood-brain barrier. With more effective therapy to the tumor cells, we expect substantially reduced side effects that the brain tumor patients currently suffer from chemotherapy treatment, and eventually improved survival and quality of life.

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Keywords: Blood-brain barrier, plasmonic nanobubble, drug delivery, tight junction.

Photothermal Heat Generation of Gold Nanorods and Gold Nanoshells for Laser Nanowarming

Poster Presentation. NEMB2018-6216

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1064 nm pulsed laser heating of gold nanoparticles can induce ultrafast heating rate on the order of 107 °C/min1. This can be used to treat cancer as has been extensively studied2,3, or more recently to enhance the rewarming of vitrified systems1. For instance, low concentration cryoprotective agent (i.e. 2 ? 3 M CPA) vitrified cells or embryos require fast rates of warming compared with traditional convective warming to survive the warming1. Understanding the plasmonic interaction of gold nanoparticles with millisecond pulsed 1064 nm lasers is of great importance for optimizing this nanowarming process through nanoparticle selection, developing heating models, and improvement on heating procedures.

However, there is limited knowledge to accurately predict the photothermal conversion properties of different gold particles in complex chemical and physical environments during this process. In this study, the photothermal heat generation of hollow gold nanoshells (225nm diameter), gold nanoshells with silicon core (198 nm inner diameter, 21 ? 22 nm shell thickness) and gold nanorods (86.5 ? 92.8 nm length, 14 ? 15.4 nm width) are quantitatively compared experimentally and theoretically in both aqueous and propylene glycol (CPA) solutions.

More specifically, the effects of 2 M propylene glycol concentration and sonication time on the stability, biocompatibility and photothermal heat generation of different gold nanoparticles are investigated. Compared with the nanoshells in aqueous solutions, the tested gold nanorods are found to have higher photothermal conversion efficiency but a lower absorption cross section at the laser wavelength of 1064nm. When normalized by the effective geometric cross section, the absorption efficiency of the gold nanorod (86.5 nm length) is almost twice of that for the tested gold nanoshells. More results and discussion will be presented during the poster session. We believe the obtained data and conclusions will help develop mature nanowarming technology.

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A Numerical Investigation of the Cyclic Pulsing Paradigm for Irreversible Electroporation

Student Competition Presentation. NEMB2018-6221

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Objective: Clinical application of Irreversible Electroporation (IRE) is becoming increasingly popular for the ablation of nonresectable tumors. IRE therapy is induced through the application of short (~100?s), high voltage (1000-3000V) pulsed electric fields and results in nonthermal cell death and the preservation of underlying tissue scaffolding, blood vessels, and nerves. Although effective, the application of excessive pulsing can result in thermal damage of tissue immediately surrounding the electrodes (~1-5mm). Current thermal mitigation strategies necessitate the use of modified electrodes and utilize coolants or latent heat storage systems as a means to achieve lower treatment temperatures. Therefore, we aim to study the thermal mitigation effects of a novel cycled pulsing paradigm for IRE therapy. Methods: We implement the finite element method to quantify increases in temperature due to Joule Heating associated with each cycled pulsing scheme. For each cycled pulsing scheme, the total number of pulses per probe pair was conserved to 80 pulses. Pulse sets of 5, 10, 20, 40, or 80 pulses were cycled until a total of 80 pulses were applied between each probe pair. Additionally, delays of 0, 5, 10, or 20s were incorporated between pulsing sets. Results: The implementation of any cycled pulsing scheme resulted in a decrease in the computed thermal damage volume. Most notably, implementing a 5 pulse, 0s delay scheme resulted in a 47.3% decrease in thermal damage volume compared to the standard 80 pulse, 0s delay scheme. Incorporating 0s delay after each probe pair results in lower thermal damage while maintaining the same theoretical treatment time. Incorporation of a delay (5s, 10s, 20s) resulted in less thermal damage, although the delays increased total treatment time. Conclusion: The cycled pulsing paradigm is a novel thermal mitigation strategy that demonstrates effectiveness in reducing damaging effects of Joule Heating.

Evaluation of Biomarkers for Circulating Osteosarcoma Cell Isolation using Microfluidics

Poster Presentation. NEMB2018-6225

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Osteosarcoma (OS) is the third most common adolescent cancer. Despite its rarity, OS is particularly lethal and 80% of patients will have clinically undetectable micro metastases. Immunoaffinity isolation of circulating tumor cells (CTCs) has been effective in detecting metastatic cancer in a variety of cancer types. Immunoaffinity-based CTC isolation often utilizes Epithelial Cell Adhesion Molecule (EpCAM) to isolate CTCs from the blood stream, which might not be expressed on the surface of OS CTCs. We report our study on a panel of potential markers as potential targets for immunoaffinity OS CTC isolation.

We utilized flow cytometry and microfluidic devices to study a panel of biomarkers for OS CTC isolation. Disialoganglioside 2 and 3 (GD2, GD3) are highly expressed and conserved biomarkers present in metastatic OS. EpCAM was included in our panel as a standard of a clinically useful CTC marker. We employed five OS cell lines to check for cell surface marker expression and their isolation in microfluidic devices. For flow cytometry, cells were prepared as a solution of 3x105 cells and then conjugated with fluorescently-labeled antibodies against these biomarkers. If a cell expresses a biomarker of interest, the cell will show a fluorescence signal in flow cytometry due to antigen-antibody conjugation.

Microfluidics-based immunoaffinity studies were carried out by using a herringbone-mixer-based device. Antibodies were bound to the inner surface of microchannels in the device using avidin-biotin chemistry. Solutions of 105 cells in 1 mL of a phosphate-buffered saline (PBS) solution were pre-stained before being passed through devices at 1 μL/s. After washing, cells captured in the device were counted via fluorescent microscope.

Our results suggest that EpCAM is a poor biomarker for OS CTC immunoaffinity isolation in microfluidic devices. The highest capture efficiency for our OS cell lines was 15.9% in our capture studies using EpCAM, which was significantly lower than our capture efficiency using BxPC3 cells, a pancreatic cell line known to express EpCAM. These results agreed with our flow cytometry data, as OS cell lines showed poor EpCAM expression. GD2 and GD3 showed good cell surface expression in OS cells based on flow cytometry and microfluidics-enabled cell capture, respectively. We believe that GD2 and GD3 could be suitable markers for immunoaffinity-based OS CTC isolation. Future studies will evaluate the efficacy of GD2 and GD3 as cell surface markers to detect OS CTCs using in vivo models.

Fluitrode: individually programmable biopolymer membrane arrays to assemble, intercept and release synthetic ecosystems

Student Competition Presentation. NEMB2018-6233

***Seyed Ali Rooholghodos, Phu Pham, John Choy, Xiaolong Luo**, Catholic University of America, Washington, DC, United States*

In natural ecosystems, interactions among microorganisms occur extensively in the forms of metabolite trading or intercellular signaling to help each other survive or compete. Modeling the complex interactions of natural ecosystems in an artificial and controlled environment is of great interest for the development of new biological technologies. Microfluidic platforms have been of great interest in providing three-dimensional cell culture scaffold and facilitating the control and monitoring of in vitro interactions between cells and with extracellular matrix. Challenges remain in culturing cells with a spatial resolution that mimics the natural ecosystems and enables the complex interactions among microbial communities. In this study, we present a novel microfluidic platform to address this pressing need. We designed and microfabricated a polydimethylsiloxane (PDMS) microfluidic device that enables the assembling, interception and releasing of multiple cell populations in 3D hydrogels of spatial and biological relevance. The device is composed of one middle microchannel and 12 individually-addressable side microchannels that are each connected with the middle channel with a small apertures (50 μm in all three dimensions). Freestanding and semipermeable biopolymer chitosan membrane arrays, termed as fluitrodes, were biofabricated in these apertures. Like electrodes in transmitting electrons, the fluitrodes allow the transmission of ions and small molecules from one microchannel to another.
Calcium alginate hydrogels were cross-linked by calcium ions diffusing through fluitrodes to embed target cells in adjacent gel layers along a single fluitrode, or in gel on proximal fluitrodes. Complex interactions between multiple species within a microbial community can be established and studied. We successfully demonstrated that six populations of cells were sequentially assembled populations in 3D hydrogels on fluitrodes side by side. The spatial resolution of cell popultions was in tens to hundreds of micrometers, the length scale of biological relevance. The fluitrodes allow for the controlled delivery of nutrients and chemical molecules of interest, live imaging of in-situ biological events, effluent collection to perform ex-situ diagnostics, and finally, cell release for downstream molecular and biochemical analyses.
This novel cell co-culturing platform models the ecosystems that are comprised of multiple species, allows for interception of the interactions in complex communities, and aids in high throughput screening for drug discovery. Currently we are studying the mutual interactions between P. aeruginosa bacteria and S. cerevisiae yeast, and we expect the fluitrode platform to be a significant tool for many biological studies.

Lateral Cavity Acoustic Transducers: A Novel Platform For Applying Mechanical Stimuli On Cells With Simultaneous On-Chip Pumping

Poster Presentation. NEMB2018-6246

***Mohammad Aghaamoo, Neha Garg, Xuan Li**, University of California Irvine, Irvine, CA, United States*, ***Abraham Lee**, University of California At Irvine, Irvine, CA, United States*

Mechanical stimuli are among the key factors affecting cell behavior. For many years, biologists and biomedical engineers have applied mechanical stimuli on cells to study their biological responses such as growth, gene expression, intracellular uptake, etc. In recent years, there has been growing interest in the use of microfluidics technology to apply mechanical stimuli on single cell level and with precise and high throughput manner.
Although so many promising microfluidics methods have been developed for this purpose, the field still needs further improvement as the current methods are either low throughput or suffer from high complexity. Here, we present a single device platform, based on lateral cavity acoustic transducers (LCATs), that can apply tunable shear stresses and consequently shear-induced deformations on cells. The oscillating liquid-gas interfaces in LCATs result in acoustic microstreaming vortices in the device. The cells that are trapped in these vortices experience shear stresses that can be varied by the changes in the interface oscillation controlled by the piezoelectric transducer (PZT) voltage. In addition, the slanted angle of LCATs provides the device with pumping the bulk flow that eliminates the need for external pumping. LCAT provides a simple way to apply wide range of shear stresses and shear-induced deformations on cells. This technique can subject the cells to the mechanical stimuli for any duration without trapping them physically or passing them through a very long microchannel.

High throughput islet cryopreservation using 3D printing and laser warming.

Student Competition Presentation. NEMB2018-6254

***Li Zhan, Shuangzhuang Guo, Kanav Khosla, Erik Finger, Michael McAlpine**, University of Minnesota, Minneapolis, MN, United States*, ***John Bischof**, Univ Of Minnesota, Minneapolis, MN, United States*

Diabetes has a considerable adverse impact on the health, wellbeing, and longevity of affected individuals, specifically in the US, with 9.4% of the population diagnosed with diabetes, moreover, 1 in 4 healthcare dollars is spent on treating diabetes in 2017. Islet transplants hold the potential to cure diabetes and restore normoglycemia, however, frequently require two or three donors, for example, more than 100,000 islets, to achieve insulin independence. Therefore, a method for high throughput ?banking? of islets could greatly improve the manner in which these limited availability resources are utilized for transplant, for instance, changing the process from an unscheduled urgent event to a planned elective procedure. Recent progress using vitrification (formation of a glass as opposed to crystalline ice) along with laser nanowarming (outrunning ice formation during rewarming) has successfully cryopreserved small oocyte systems (i.e., 100um diameter) and large zebrafish embryos (i.e., 800um diameter) with low cryoprotective agent (CPA) concentration (<3 M).
Unfortunately, to translate this promising technology for clinical application such as islet transplants, high throughput platform technologies for ultra-fast cooling and rewarming are still missing. Herein, we developed a 3D printing technology for high throughput vitrification of islets in 3 M CPA with current yield of 200 islets/min, which can be further scaled up to 10,000 islets/min. Specifically, islets will be first loaded with CPA and gold nanorod (GNR) with optimized protocols, a ?pick & print? method will be used to pick up pancreatic islets from the petri dish where they were loaded and printed onto a cryogenic copper dish. More specifically, by handling one droplet at each time? Pick & print? Overcomes tip blockage due to pancreatic islets settling in conventional printing method where pancreatic islets and culture media are loaded into the syringe for direct printing. And importantly, this? Pick & print? Technique possesses the ability to tune droplet size by varying pressure and time during picking process. This control in volume is important as it allows the optimization between pancreatic islets printing efficiency and faster cooling rates that favor vitrification. X ray diffraction measurement at -173C confirmed the amorphous state of the droplets. We have also developed a modified? cryoscoop? To transfer the droplets under laser for rewarming. In addition, we are developing of an automatic robotic system to achieve high throughput laser warming. Such technology could enable long term banking of islets for transplant and revolutionize how islets are recovered, allocated, and utilized.

Skeletal Muscle Reprogramming with Microfluidic Mediated Controlled Drug Release

Poster Presentation. NEMB2018-6257

***Jun Fang**, UCLA, Los Angeles, CA, United States*, ***Jaekyung Koh**, UCLA, LA, CA, United States*, ***Dino Di Carlo, Song Li**, University of California, Los Angeles, Los Angeles, CA, United States*

Skeletal muscle has a remarkable ability to repair after minor injury, mediated by a resident population of satellite cells. However, their self-renewal potential is limited and further compromised with aging, excessive trauma, or genetic defects. Direct reprogramming somatic cells into alternative lineages have highlighted a promising strategy for regenerative therapy, via defined factors including transcription factors, RNA, proteins, and small molecules. Among them, small molecules offer powerful tools for manipulating cell fate in cell reprogramming. Meanwhile, material/physical cues suggest other exciting possibilities in specifying cell behaviors.

Here, we screened a cocktail of chemicals for direct skeletal muscle reprogramming, and developed a novel particle-micro gel system to control the release of the small molecules for cell reprogramming, which has potential for in situ cell regulation for tissue regeneration.

Fabrication of the nano/micro patterned conductive scaffold coated by poly(pyrrole) for neural regeneration

Poster Presentation. NEMB2018-6266

Ji Hong Min, Won-Gun Koh*, Yonsei University, Seoul, Korea (Republic)*

This study is to produce the surface-patterned scaffold coated by PPy poly(pyrrole) that can provide nerve cells with morphological and electrical stimuli for nerve regeneration. For nerve regeneration, it is necessary to provide a similar environment in which neurons can proliferate well to connect damaged nerves. To provide physical stimulation to nerve cells, an aligned pattern was made of PVP (poly(vinylpyrrolidone)) electrospun fibers on the surface of biodegradable scaffold. Also, in order to provide electrical stimulation, PPy was coated on the prepared scaffold to make a conductive scaffold which can provide electrical stimulation to the surface. It is expected that the fabrication technique of this scaffold can be applied to regenerate the nerve tissues naturally in tissue engineering area.

Fabrication and Multiphysics Modeling of MEMS Thermal Flow Sensors

Student Competition Presentation. NEMB2018-6269

Justin Cable*, Calif. State Polytechnic Univ. at Pomona, Pomona, CA, United States*, ***Kevin Anderson****, California State Polytech Univ, Pomona, CA, United States*

The miniaturization, biocompatibility, sensitivity and versatility achieved with thermal flow sensors has drawn interest in multiple engineering disciplines. Multiple configurations of a micromachined thermal flow sensors are presented demonstrating a liquid flow rate on the scale of microliters per minute capable of being used for drug delivery systems like insulin pumps, chemical compound mixing, gas chromatography, or various other biomedical applications. These flow sensors relay the varying electrical signals of sensors created by the heat transfer generated by different flow rates. The sensor arrays presented were constructed using microelectromechanical systems (MEMS) techniques including micro-molding, wet etching and dry etching utilizing biocompatible materials.   A numerical model was built using COMSOL multi-physics in order to predict and describe the electrical, thermal and fluid behavior of the sensor, which was later verified with experimental data. The array of sensors was used to characterize the heat distribution created by a resistive heater and compared to the simulations and existing analytical solutions. This method is known as the calorimetric sensing principle and is one of 3 major thermal flow sensing methods. The construction allowed for multiple thermal flow sensing operational modes including hot-film, calorimetric, and time-of-flight without changing the design.
The calorimetric sensing principle has been shown to have superior sensing capabilities. For this reason, the heat distribution around a centralized heater between several temperature sensors was thoroughly investigated. The variety of flow sensor geometries constructed were compared to investigate maximum heat transfer to the sensors, thermal insulation, size, sensitivity and range capabilities. Performance characterization for the sensor used measurement uncertainty theory to reflect the probability distribution of measured flow rate data as they relate to the ?actual? values. The frequency response was also experimentally derived and investigated to demined governing factors. The sensor design is such that it is capable of detecting different flow direction and various flow ranges for different fluids. In addition to the performance capabilities outlined, the sensor is relatively inexpensive and should have a long lifetime due to the lack of moving parts. Lastly, the final assembly can then be mounted onto a printed circuit board for easy electrical connections.

Site Selective Nucleation and Growth of Gold Nanoparticles on the Pore Structures of a Virusabs

Student Competition Presentation. NEMB2018-6272

Candace Benjamin, Zhuo Chen, Peiyuan Kang, Blake Wilson, Na Li, Steven O. Nielsen*, The University of Texas at Dallas, Richardson, TX, United States*, ***Zhenpeng Qin****, Univ of Texas At Dallas, Richardson, TX, United States*, ***Jeremiah J. Gassensmith****, The University of Texas at Dallas, Richardson, TX, United States*

Site specific delivery of drug molecules to target tissues provides a means for effective dosing while possibly reducing the adverse side effects often associated with systemic drug administration.

To achieve this specificity in delivery, we have employed the virus-like particle (VLP) Q? as a proteinaceous drug carrier capable of release via precise external stimulus. We have shown that this viral capsid is capable of holding upwards of 500 molecules of the anti-cancer drug Doxorubicin within its genetic material. Additionally, using gold?s natural affinity for sulfur, the VLP provides a template for the facile synthesis of ~6 nm gold nanoparticles. The complete system allows for payload release upon stimulation by a single six nanosecond pulse green laser. We hypothesize that the laser energy is absorbed by the gold nanoparticles which is then converted to thermal energy that denatures the protein capsid releasing the encapsulated Doxorubicin. This system denoted as Q?(Dox)@AuNP has been tested in RAW 264.7 macrophages and have been shown to exhibit uptake and release such that a) the laser light itself does not harm cells and b) when masked, cells containing Q?(Dox)@AuNP only release Dox if present in the
laser path of green laser.

Increasing PRP Concentration is Associated with Improved Metrics of Acellular Dermal Matrix Incorporation.

Poster Presentation. NEMB2018-6275

Raquel Araujo-Gutierrez, Jeffrey Van Eps*, Houston Methodist Hospital, Houston, TX, United States*, ***Fernando J Cabrera, Keith A Youker****, Houston Methodist Research Institute, Houston, TX, United States*, ***Joseph Fernandez-Moure****, University of Pennsylvania, Phladelphia, PA, United States*

Introduction: Platelet rich plasma (PRP) has been shown to improve incorporation and reduce CD8+ cell infiltration in ventral hernia repair (VHR) with acellular dermal matrix (ADM). The concentration of platelets in PRP varies in studies and a standardized concentration has yet to be defined. Thus, we sought to study the effects of varied concentrations of PRP on ADM incorporation and CD8+ cell infiltration in a rat model of VHR. We hypothesized that increasing concentration of PRP would lead to improved incorporation and decreased CD8+ cell infiltration.
Methods: Lewis rats underwent ventral hernia creation and repair 30d later with porcine non-crosslinked ADM. PRP was applied to the mesh prior to skin closure at concentrations of 1x104plt/?l (LOW-plt), 1x106plt/?l (MID-plt), or 1x107plt/?l (HIGH-plt) and tissue harvested at 2 and 4wks. Cellularization, tissue deposition, and mesh degradation were quantified using H&E and Massons trichrome. Neovascularization was assessed with VVG staining. Inflammatory cell infiltration was assessed using immunohistochemical staining for CD45 and CD8.
Results: ADM treated with HIGH-plt showed greatest tissue deposition and lowest scaffold degradation at 4wks. Cell infiltration was significantly higher with HIGH-plt at both time-points. While, non-significant, neovascularization was highest with MID-plt at 2wks. No differences were shown in CD8+ cell infiltration.
Conclusion: Increasing platelet concentrations in PRP correlated with improved incorporation, tissue deposition and decreased scaffold degradation but no difference in inflammatory cell infiltrate. These findings suggest increasing the number of platelets in PRP may be beneficial for ADM incorporation in VHR but more work is needed to define the ideal concentration and dose.

Trapping Exosomes Using Acoustic Microstreaming for Point-Of-Care Diagnostics

Poster Presentation. NEMB2018-6276

Iember Hemben*, University of California Irvine, Irvine, CA, United States*, ***Abraham Lee****, University of California At Irvine, Irvine, CA, United States*, ***Neha Garg****, University of California Irvine, Irvine, CA, United States*

Point-of-care diagnostics has the potential to provide low-cost, low sample experimental assays to people in need, greatly reducing the time and cost required for effective disease prognosis. Many experiments that traditionally require a large blood sample and a bench top environment can be completed using only a drop of blood and a microfluidic device. However, the complex composition of human blood causes challenges in the analysis of whole, undiluted blood. We have developed a multi-functional microfluidic acoustic streaming platform titled lateral cavity acoustic transducer (LCAT), that provides a single device solution to the sorting, enrichment and in situ labeling of whole blood. LCAT can perform the following on whole blood: sorting into cellular subsets (platelets, RBCs, and WBCs), enrichment and retrieval of breast cancer cells, and on-chip immunofluorescent labeling for detection of specific target cell populations. Based on evidence that exosomes such as proteins and microRNAs are closely associated with most disease and could potential serve as a reliable biomarker for disease diagnosis and therapy, we aim to expand the capabilities of the LCAT device to include the trapping of extracellular components such as exosomes for disease diagnosis.

The mechanism behind LCAT is based on the liquid-gas interfaces formed by air trapped in dead-end side channels. When this interface oscillates, it creates two streaming flows: a second-order characteristic streaming viscous flow velocity (U_s) and a bulk flow (U_b). There is a critical open streamline that borders the closed streamline at end of the liquid-air interface vortex. In between this open and closed streamline is a gap titled d_{gap}, and particles larger than the d_{gap} are trapped within the vortex. The equation for the d_{gap} is as follows: $d_{gap} = (U_b/U_s) * (W/2)$, where U_b is the bulk streaming velocity, U_s is the streaming viscous flow velocity, and W is the width of the channel. By adjusting the geometry and flow velocity ratio of the lateral cavity channels to reduce the d_{gap}, we propose that the LCAT can be used to trap exosomes, further demonstrating LCAT as a multi-functional microfluidic platform for blood-based disease diagnosis and prognosis.

Lipid Bilayer Droplet as a GARP-Expressing Artificial Antigen Presenting Cell

Poster Presentation. NEMB2018-6277

***Jui-Yi Chen, Shih-Hui Lee**, UC Irvine, Irvine, CA, United States*, ***Abraham Lee**, University of California At Irvine, Irvine, CA, United States*, ***Anshu Agrawal**, University of California, Irvine, Irvine, CA, United States*

Inflammation defends he body against pathogens and helps the healing of damaged cells. During inflammation, the binding of antigens on the antigen presenting cells (APC) and the T cell receptor (TCR) on the T cells leads to T cell activation and expansion. While T cell activation is essential to protective immunity, without a proper control, it can cause chronic inflammation or autoimmune diseases. GARP-expressing APC has demonstrated great effect in activating regulatory T cells (Treg) that down-regulate the immunoresponse.

Artificial antigen presenting cells (aAPC) have emerged as an effective way to modulate the immunoresponse. To effectively activate T cells, membrane fluidity and size of aAPC are of major concern. While the current aAPC can successfully express antigens on the surface, most of them fail to come in the recognizable sizes and lack fluidity. In this study, we present the generation of aAPC by a double emulsion method. The aAPC proposed here is a lipid bilayer droplet with GARP conjugated on the surface (GARP-aAPC). The aAPC has been shown to be uniform, stable, and biocompatible. The synthesized GARP-aAPC will be cultured with CD4 T cell purified from human peripheral blood mononuclear cell (PBMCs). IL-10, IFN-? and TGF-? will be assayed to evaluate the induction of Treg. The optimized GARP concentration and the droplet concentration for Treg activation will be presented. The development of GARP-aAPC opens up a new realm for the treatment of autoimmune diseases and could serve as a tool for manipulating immune system.

WEDNESDAY, AUGUST, 22

TRACK 7
Plenary Speakers

7-2
PLENARY SESSION II
Los Angeles, OMNI Hotel, Bunker Hill Room 8:00am - 8:50am

Session Organizer: **Abraham Lee**, *University of California At Irvine, Irvine, CA, United States*

Technologies for Personalizing Cancer Immunotherapies
Plenary. NEMB2018-6283

***James Heath**, Institute for Systems Biology, Seattle, WA, United States*

At the heart of most cancer immunotherapies are specific molecular interactions between the principle cancer cell killers, T cells, and the tumor-associated peptide antigens that are presented within the tumor environment. Knowledge of these molecular details can provide deep insight into the nature of which patients do and don?t respond to therapies, as well as guidance for designing therapies that range from vaccines to engineered T cells.
I will discuss a number of single cell methods aimed at extracting the tumor-specific T cell receptor (TCR) ?/? genes and the peptide-major histocompatibility complexes (pMHCs) that they recognize. A more subtle challenge involves identifying those TCR-pMHC interactions that lead to activated T cells. It is not just the strength of the TCR-pMHC complex, but rather the lifetime of that complex, that is important. I will further discuss large scale molecular dynamics simulations we have carried out to identify a structural mechanism that uncouples TCR signaling from pMHC binding, and may provide insights into the exquisite sensitivity that characterizes these critical immuno-oncology interactions.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-3
IMMUNOTHERAPY AND DRUG DELIVERY I
Los Angeles, OMNI Hotel, Museum A 9:00am - 10:20am

Session Organizer: **Robert Ivkov**, *Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Nanomedicine approaches to improve cancer immunotherapy
Keynote. NEMB2018-6141

***Andrew Wang**, University of North Carolina Chapel Hill, Chapel Hill, NC, United States*

Cancer immunotherapy, the utilization of the patients? own immune system to treat cancer, has emerged as a powerful new strategy in cancer treatment. The development of antibodies that can block negative immune regulatory pathways, such as the cytotoxic T-lymphocyte?associated antigen 4 (CTLA-4) and the programmed cell death 1 (PD-1) pathways, have resulted in clinical improvements in patients that have not been seen previously. esophageal, and head and neck cancers. Despite the successes of checkpoint inhibitors, a major limitation of cancer immunotherapy has been the low long-term durable response rate and low complete response (CR) rate. Given the observation that patients who develop a response to cancer immunotherapy have prolonged survival compared to the patients who do not, there has been high interest in developing strategies to further improve cancer immunotherapy.

In this session, we will discuss two approaches that our group has developed to improve cancer immunotherapy. One approach is to utilize antigen-capturing nanoparticles to capture tumor antigens that are released after radiotherapy. We showed that these nanoparticles highly effective in antigen presentation and can improve immunotherapy response. We will also discuss our recently reported dual immunotherapy nanoparticles. By presenting immunotherapy agents to T cells simultaneously, we demonstrated that we can significantly improve the treatment response over standard immunotherapy combinations.

Cold responsive nanoparticle for overcoming cancer drug resistance
Technical Presentation. NEMB2018-6229

***Xiaoming He**, University of Maryland, College Park, MD, United States*

Although nanoparticle-mediated delivery of therapeutic agents has been widely studied for thermal therapy utilizing high temperature to destroy tumor for many years, it has not been explored in the field of cryobiology until recently. We have developed novel cold-responsive nanoparticles that release their payload in response to cooling to below room temperature. These nanoparticles encapsulated with anticancer drugs in combination with ice cooling can be used to overcome cancer multidrug resistance.
This is attributed to the ice cooling induced burst drug release from the nanoparticles and minimization of cell metabolism. The former surpasses the rate of drug efflux via the transmembrane efflux pumps overexpressed in multidrug resistant cancer cells, and the latter compromises the function of the efflux pump by minimizing the synthesis of ATP that drive the efflux pumps. Moreover, these nanoparticles are shown to preferentially accumulate in (i.e., target) tumor after intravenous injection. When combined with ice cooling, these nanoparticles efficiently inhibit the growth of multidrug resistant tumors in vivo without evident systemic toxicity. Collectively, our novel cold-responsive nanoparticles may find tremendous applications for addressing the challenge of cancer drug resistance.

Ultrahigh Throughput Mechanoporation for Cell Delivery and Cell Therapy Applications
Technical Presentation. NEMB2018-6130

***Harish Dixit**, University of California Riverside, Riverside, CA, United States*, ***Renate Starr**, City of Hope National Medical Center, Duarte, CA, United States*, ***Daniel Nampe**, Kite Pharma, Santa Monica, CA, United States*, ***Yanyan Zhang**, University of California, Riverside, Riverside, CA, United States*, ***Christopher B. Ballas**, Indiana University School of Medicine, Indianapolis, IN, United States*, ***Hideaki Tsutsui**, UCR - Mechanical Engineering, Riverside, CA, United States*, ***Stephen J. Forman**, City of Hope National Medical Center, Duarte, CA, United States*, ***Masa Rao**, University of California, Riverside, Riverside, CA, United States*

Cancer immunotherapies, or adoptive cell transfer (ACT), have had promising results clinically and show great promise as an alternative to current therapies, such as chemotherapy or radiation. However, the methods used to genetically engineer the anti-cancer functionalities into the required cell type (T lymphocytes) possess certain drawbacks that limit them in automation and cost. There is a critical need for the development of a new cell modification strategy that addresses these shortcomings. Microinjection, which physically creates a transient membrane pore for the delivery of exogenous payloads, may represent one such solution. However, the gold standard of this technology requires significant improvement in order to be competitive against current techniques for genetic modification.

We outline preliminary efforts to develop a new form of microinjection using silicon microfabrication. To simplify fabrication procedures, and demonstrate a proof-of-concept technology, we have created a device for ultrahigh throughput (UHT) cellular manipulation via mechanical membrane poration, i.e. UHT mechanoporation. This technology represents an interim step towards our overall microinjection concept.

The fundamental nature of the device stems from a microelectromechanical systems (MEMS) functional core composed of cell capture sites with monolithically integrated, sub-micrometer scale solid penetrators. Negative flow through aspiration vias at the bottom of the capture sites pulls cells onto the penetrators thus causing membrane poration. Cells are then released by reversing flow through the aspiration vias. The transient nature of membrane disruption enables transfection via diffusion-driven influx of exogenous molecules from the surrounding suspension, while massive parallelization provides for UHT operation (e.g. 10k capture sites in the current device).

Though our original studies validated concept feasibility, low cell treatment efficiencies were observed (~8%). Herein, we describe our recent work on increasing the efficiency of our MEMS-based UHT mechanoporation devices. The implementation of high-resolution fluorescence imaging during device operation and precise flow rate control in the aspiration circuit has provided a means for improved device characterization. Through our efforts, we have been able to increase our efficiencies by optimizing several device parameters. We have found that improved washing steps, specific flow rates for capture and penetration, and the addition of an immobilization step during our wash cycle significantly improved the proportion of concurrently porated and viable cells in the collected population. These improved parameters thereby increased our cell treatment efficiency nearly 12 fold (~90%). Collectively, such results demonstrate the potential of cellular poration techniques to address limitations in ACT, and have helped to identify directions for future device development.

TRACK 2
Nano/micro fluidics

Track Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*
Track Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

2-1
LAB ON A CHIP SYSTEMS FOR SINGLE CELL BIOLOGY
Los Angeles, OMNI Hotel, Museum B
9:00am - 10:20am

Session Organizer: **Rong Fan**, *Yale University, New Haven, CT, United States*
Session Co-Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*

Single-cell proteomics microchip for monitoring cancer immunotherapy
Keynote. NEMB2018-6210

***Rong Fan**, Yale University, New Haven, CT, United States*

Despite recent advances in single-cell genomic, transcriptional and mass cytometric profiling, it remains a challenge to collect highly multiplexed measurements of proteins produced from single cells for comprehensive analysis of immune functional state. My talk will be discussing a novel microchip technology for single-cell proteomic profiling, in particular, the co-detection of 40+ immune effector proteins such as cytokines/chemokines at the level of single cells, representing the highest multiplexing recorded to date for a single-cell protein secretion assay. I will describe how this microchip technology called IsoCode was conceived at the beginning, evolved over generations, further integrated with a fully automated single-cell processing platform called IsoLight comprising high-resolution optics, precision fluid handling and live cell incubation in the same system to truly enable robust and reproducible functional proteomics data at the single-cell level. It has been in the pipeline of commercialization at IsoPlexis and adopted by pharmaceutical companies like Novartis, Kite Pharma (a Gilead Company), Bellicum, and many others to evaluate their immunotherapy products. This microchip technology allowed for the full-spectrum dissection of T cell functions including genetically engineered chimeric antigen receptor T cells (CAR-T) in the treatment of patients with acute lymphoblastic leukemia or non-Hodgkin?s lymphoma. Our data obtained from a medium-scale clinical trial with CD19 CAR-T cells demonstrated strong association between CAR-T cells? polyfunctionality (the ability for a single T cell to co-produce multiple immune effector proteins) and patient response, which opens up new opportunities for predicting not only therapeutic efficacy but also potentially life-threatening immunotoxicity. All these underscore the importance to measure functional proteomic heterogeneity even in phenotypically identical cell populations in order to evaluate the quality of cell-based therapeutics or to monitor patient responses for precision medicine.

A Multiplexer-Based Addressable Micro-Trap Array for Droplet Discretization and Manipulation
Technical Presentation. NEMB2018-6182

***Hesam Babahosseini, Tom Misteli**, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States*, ***Supriya Padmanabhan, Don L. DeVoe**, University of Maryland, College Park, MD, United States*

Droplet-based microfluidic technology has been emerged recently as a powerful tool to carry out a broad range of applications in biomedical diagnosis, drug screening, biochemical analysis, and micro-biosynthesis. Droplet-based micro?uidics provide a new approach for the generation and manipulation of nano- to pico-liter scale aqueous droplets in space and time.
In this study, we developed an innovative microfluidic platform enabling discretization and manipulation of aqueous droplets. The microfluidic platform integrates a micro-traps array, all connected to a main microchannel for fluid delivery and simple displacement membrane elements for controlled manipulation (i.e. retrieval, metering, or merging) of droplets. The droplets are formed by discretizing sample into pico-liter scale volumes of the micro-traps. .
The formed droplets are in the static mode for easy screening or long-term incubation. The droplets are individually addressable and can be precisely and reliably manipulated by the separate displacement membrane elements embedded to thoroughly cover the micro-traps. The elastomer membrane can be deflected into a micro-trap under a high air pressure to displace the stored droplet into the main microchannel. The displacement membrane elements are controlled using a microfluidic multiplexer which minimizes the required number of control lines for achieving a highly scalable micro-traps array. The microfluidic multiplexer can selectively open/pressurize a control line connected to individual displacement membranes by means of intersecting blocking lines.
The microfluidic PDMS platform is manufactured by multi-layer soft-lithography, integrating fluidic, membrane, and control layers. The fluidic layer consists of the micro-trap array, the main microchannel, and the blocking lines, and the control layer contains pneumatic control lines for micro-valve actuation. Both layers are fabricated by PDMS molding from fabricated SU-8 masters. The membrane layer, which serves to form the displacement membrane elements and the multiplexer micro-valves, the deformable structures upon application of a positive pressure in the control lines, is obtained by spin-coating the PDMS on a SU-8 master mold. The microfluidic platform was operated by a solenoid valve manifold and an Arduino microcontroller board for selectable addressing the displacement membrane elements through the microfluidic multiplexer.
The described integrated platform allows for the execution of droplet formation in an addressable micro-trap array, together with consecutive manipulation of stored droplets for controlled retrieval, metering, or merging of selected droplets. This droplet-based microfluidic technology can be evolved as an alternative to the traditional multi-well plates with higher efficiency (i.e. reduced reaction volume, time and cost), enabling diverse applications in biological and biochemical sciences.

A Droplet Microfluidic System for Screening T-cells Bearing Specific TCR for Target Tumor Antigen
Technical Presentation. NEMB2018-6191

***Aude Segaliny, Xiaoming Chen, Lingshun Kong, Ci Ren**, University of California Irvine, Irvine, CA, United States*, ***George Wu**, amberstone biosciences, Irvine, CA, United States*, ***Weian Zhao**, University of California, Irvine, Irvine, CA, United States*

Screening T-cells bearing some specific TCR has become one of the most popular methods for cancer treatment. The screening process has to be addressed on the single-cell level due to cell heterogeneity. Traditional cell screening methods typically use a microtiter well plate combined with a robotic system for single cell dispensing, which is quite expensive, but low throughput.
This work develops a droplet microfluidic system for screening T-cells, which is capable of performing real-time single cell monitoring and recovery with high throughput in the scale of 10,000. First, a single T-cell and single cancer cell are encapsulated into a sub-nanoliter droplet. Then, droplets are loaded into a floating drop array which has ~30K trapping wells for real-time monitoring over 9 hours. After that, droplets containing the target T-cells can be kicked out of the trapping wells using laser induced cavitation. Finally, the recovered single target T-cell is dispersed into a PCR tube for performing scPCR (single cell PCR) to verify the sorting accuracy. Compared to the traditional microtiter well plates, this droplet microfluidic system dramatically increases the single cell analysis throughput, and reduces the analysis time and cost.

Microfluidic Device with Embedded Microporous Nylon Membranes for Efficiently Filtering and Dissociating Digested Tissue into Single Cells
Technical Presentation. NEMB2018-6163

***Xiaolong Qiu, Jeremy A. Lombardo**, University of California, Irvine, Irvine, CA, United States*, ***Trisha M. Westerhof**, University of Michigan, Ann Arbor, MI, United States*, ***Edward L. Nelson, Elliot E. Hui, Jered B. Haun**, University of California, Irvine, Irvine, CA, United States*

Tissues are increasingly being analyzed at the single cell level in order to characterize cellular diversity and identify rare cell types. Single cell analysis efforts are greatly hampered, however, by the need to first break down these tissues into a single cell suspension. Current dissociation methods are inefficient, leaving a significant portion of the tissue as aggregates that are filtered away or left to confound results. Here, we present a simple and inexpensive microfluidic device that simultaneously filters large tissue fragments and dissociates smaller aggregates into single cells, thereby improving both single cell yield and purity. .

The device incorporates two nylon mesh membranes with well-defined, micron-sized pores that filter and dissociate aggregates of different dimensions. We also designed the device so that samples could encounter the first membrane under a tangential flow format to minimize clogging. Using cancer cell lines, we demonstrated that aggregates were effectively dissociated using high flow rates and pore sizes that were comparable to or smaller than single cells. However, the small pore sizes also decreased viability in proportion to the extent of dissociation We then demonstrated that single cell yield and purity were improved by connecting two filter devices in series, with results dictated primarily by the pore size of the second membrane. Next, we optimized performance using minced and digested murine kidney tissue samples, and determined that the combination of 50 and 15 μm membranes was optimal. Finally, we integrated these membranes into a single filter device and performed validation experiments using minced and digested murine kidney, liver, and mammary tumor tissue samples. These tests indicated that the microfluidic filter device increased single cell numbers by at least 3-fold for each tissue, with no change in viability. Notably, the filter devices often produced similar numbers of single tissue cells after a brief 15 min enzymatic digestion as controls after a longer 60 min digestion, which holds exciting potential to accelerate tissue processing work flows and preserve the natural phenotypic state of cells. We also observed that tangential flow reduced clogging, but did not affect single cell numbers. In future work, we will integrate the microfluidic filter device with additional upstream tissue processing technologies, as well as downstream cell sorting and analysis operations.

TRACK 6
Nanophotonics for biomedical imaging

Track Organizer: **yadong yin**, *University of california riverside, Riverside, CA, United States*
Track Co-Organizer: **peter yingxiao wang**, *UC San Diego, La Jolla, CA, United States*

6-1
BIOIMAGING IN LIVE CELLS
Los Angeles, OMNI Hotel, Hershey
Room 9:00am - 10:20am

Session Organizer: **Min Xue**, *UC Riverside, Riverside, CA, United States*
Session Co-Organizer: **Jin Zhang**, *UC San Diego, La Jolla, CA, United States*

Illuminating the Biochemical Activity Architecture of the Cell
Keynote. NEMB2018-6222

***Jin Zhang**, UC San Diego, La Jolla, CA, United States*

The complexity and specificity of many forms of signal transduction are widely suspected to require spatial microcompartmentation and dynamic modulation of the activities of signaling molecules, such as protein kinases, phosphatases and second messengers. In this talk, I will discuss the development of a series of fluorescent biosensors as well as a high throughput microscopy platform to probe the compartmentalized signaling activities.

single-cell profiling of Akt signaling dynamics in living cancer cells
Technical Presentation. NEMB2018-6206

***Shiqun Shao, Zhonghan Li, Siwen Wang, Zhili Guo, Min Xue**, UC Riverside, Riverside, CA, United States*

Cancer cells exploit abnormal cell signaling activities to achieve uninhibited proliferation. Understanding the signaling network in cancer cells is crucial for rational design and selection of effective therapeutic interventions. This task, however, is often confounded by the prominent intra- and inter-tumoral heterogeneity. Increasing evidences have demonstrated differential signaling dependencies across the same cancer type. Even within the same lesion, specific signaling activities display considerable heterogeneity, which confers selection advantages during tumor progression.

Thus, analyzing signaling activities at single-cell resolution and resolve the heterogeneous features in the sample are required to access a comprehensive understanding of tumor biology. In addition, cancer cells are capable of rewiring the signaling networks and rapidly adapt to therapeutic stresses. This property calls for a time-resolved analysis on the signaling dynamics. However, current technologies cannot fulfill this task. Existing single-cell analytical platforms require cell lysis to interrogate intracellular events and are limited to studying sample snapshots; while conventional methods for continuously probing cell signaling activities rely on genetic modifications that are unsuitable for analyzing clinical samples. Herein, we demonstrate the single-cell profiling of Akt signaling dynamics, using intracellularly delivered epitope-targeting cyclic peptides. The peptides were identified through screening of a one-bead-one-compound library. Through supramolecular interactions, these peptides specifically recognize two epitopes on the Akt protein, one of which contains a phosphorylation site that is crucial to Akt signaling. We constructed a fluorescence resonance energy transfer (FRET) pair using those peptides and delivered them into a human glioblastoma cell line (U87) using fusogenic liposomes. We show that the FRET intensity reflects the Akt phosphorylation level in living cells. We employed a micro-well based single-cell chip platform to achieve the continuous profiling of Akt signaling activities. Our results prove that cells display different levels of signaling fluctuations, and that the population-level signaling activity distribution is conserved over time. We further demonstrate the identification of resistance sub-populations by analyzing the time-resolved single cell trajectories in drug-treated U87 cells. The generalization of our strategy promises a powerful tool for probing cell signaling activities and provides a more in-depth understanding of cancer biology.

Imaging DNA Walkers with Visible/Near-Infrared Super-resolution Microscopy
Technical Presentation. NEMB2018-6162

***Feiran Li, Jing Pan, Jong Hyun Choi**, Purdue University, West Lafayette, IN, United States*

DNA walkers are designed with the structural specificity and functional diversity of oligonucleotides to actively convert chemical energy into mechanical translocation. Compared to natural protein motors, DNA walkers? small translocation distance and slow reaction rate make single-molecule characterization of their kinetics elusive. A better understanding of DNA walking mechanisms will pave the road for high-performance walker designs, which requires characterization methods with far superior spatial and temporal resolution.

In this work, we introduce a platform capable of simultaneous visible (VIS) and second near-infrared (NIR-II) subdiffraction imaging of DNA walkers. We use the super-resolution NIR-II image of an RNA decorated SWCNT as a one-dimensional (1D) track on which the translocation of a QD-decorated DNAzyme walker is imaged. Visible image is localized by fitting a 2D Gaussian function to their point spread function (PSF) while NIR-II image is constructing the difference image of consecutive frames first and then fit by Gaussian function. The localization precision on the particle position reaches ~20 nm, and precision of SWCNT track reaches ~80 nm. Using these methods, we have obtained distributions of displacement and velocity and analyzed walking randomness. With the aid of a stochastic walking model, we have identified three rate-limiting intermediate reactions in a walker stepping event.

The ability to identify and understand rate-limiting reactions from stochastic single-molecule kinetics will help formulate efficient walker mechanisms. In parallel, the super-resolution microscopy in the biologically transparent NIR-II window may be adapted for deep tissue imaging and in vivo optical sensing to access more detailed structural and dynamic information about biological systems.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-4
IMMUNOTHERAPY AND DRUG DELIVERY II
Los Angeles, OMNI Hotel, Bradbury Room
10:30am - 11:50am

Session Organizer: **Anita Penkova**, *University of Southern California, Los Angeles, CA, United States*

Engineered nanomaterials for cancer immunotherapy
Keynote. NEMB2018-6133

***James Moon**, University of Michigan, Ann Arbor, MI, United States*

Recent innovations in DNA/RNA sequencing have allowed for the identification of patient-specific tumor neo-antigens, ushering in the new era of personalized cancer vaccines. Peptide vaccines in general may serve as an ideal platform for neo-antigen vaccines, but the therapeutic efficacy of peptide vaccines have been limited in clinical trials. Here we present an alternative strategy where preformed nanocarriers, with an established clinical manufacturing procedure and excellent safety profiles in humans, are readily formulated with adjuvants and antigen peptides, including neo-antigens, to produce personalized cancer vaccines. We show that lipid-based nanodiscs can efficiently co-deliver antigen and immunostimulatory molecules to draining lymph nodes and elicit potent CD8+ cytotoxic T lymphocyte responses directed against tumor antigens, leading to substantially enhanced anti-tumor efficacy in multiple murine tumor models, including colon carcinoma, melanoma, and HPV-induced tumors. Owning to the facile production process, robust therapeutic efficacy, and good safety profiles, our novel nano-vaccine technology offers a powerful and convenient platform for patient-tailored cancer vaccination.

Evaluating Immunotoxicology, Bio-distribution, and Pharmacokinetics of DNA origami Nanostructures in vivo
Technical Presentation. NEMB2018-6149

***Christopher R. Lucas, Amjad A. Chowdury, Patrick D. Halley, Aparna Lakshmanan, Bonnie K. Harrington, Ronni Wasmuth, Larry Beaver, Rosa Lapalombella, Amy J. Johnson, Erin K. Hertlein, John C. Byrd**, The Ohio State University, Columbus, OH, United States*, ***Carlos E. Castro**, Ohio State university, Columbus, OH, United States*

Scaffolded DNA origami nanotechnology allows for the generation of pre-defined shaped nanoscale objects via molecular self-assembly as well as a robust platform for drug delivery applications. Previous studies reported that DNA origami nanostructures could be functionalized with targeting moieties and effectively loaded with anthracyclines (e.g. doxorubicin and daunorubicin) and thrombin. Furthermore, drug-loaded DNA origami nanostructures were reported to induce an enhanced anti-cancer effect relative to free drug in both solid tumor and hematologic model systems in vitro, while recent findings showed that thrombin-loaded nanostructures induce tumor necrosis and inhibit tumor growth in vivo in a targeted manner. Despite this exciting promise, the toxicology, immunogenicity, bio-distribution, and pharmacokinetics of DNA origami nanostructures in vivo remain ill defined. Here we evaluate two DNA origami nanostructures that vary in shape, a flat-2D triangle and 3D-rod-shaped nanostructure either alone or functionalized with polyethylene-glycol (PEG)-conjugated oligonucleotides. A repeat dosing regimen of unloaded triangle and rod-shaped structures at clinically relevant levels revealed that DNA origami nanostructures were generally non-toxic in vivo as shown by weight and a complete biochemical panel assessing liver function apart from mild hepatic necrosis in mice treated with PEG-coated triangle nanostructures. A modest pro-inflammatory molecular and cellular immune response was evident among mice in all treatment groups, especially among mice treated with triangle/triangle-PEG that dampened by the conclusion of the dosing regimen. Distribution findings thus far show PEG-functionalized and non-functionalized DNA nanostructures distribute throughout the periphery immediately after i.v. injection and within ~30 minutes after i.p. injection, while myeloid cell populations internalized DNA nanostructures ex vivo. We hypothesize that our PEG-functionalized DNA nanostructures will have increased stability in vivo relative to unmodified DNA nanostructures and may be evaluated via a fluorescence-based live animal in vivo imaging system (IVIS). Taken together, our in vivo findings suggest that DNA origami nanostructures are mostly non-toxic, distribute effectively into the periphery, generate a modest immune response, and, therefore represent a promising novel platform for future cancer drug delivery studies in vivo. Funded in part by start-up funds provided to Dr. Castro by the Department of Mechanical and Aerospace Engineering, The National Institutes of Health-National Cancer Institute-P50-CA140158 and R35-CA197734, The D. Warren Brown Foundation, Four Winds Foundation, and The Harry T. Mangurian Jr. Foundation. C.R.L is a recipient of a National Institutes of Health T32 Award in Oncology Training Fellowship at The Ohio State University Comprehensive Cancer Center, T32-CA009338.

Enhanced PD-1/PD-L1 Binding Kinetics via Dendrimer-mediated Multivalent Binding Effect
Student Competition Presentation. NEMB2018-6176

***Jiyoon Bu, Yun Hwa Choi, Sin-Jung Park**, University of Wisconsin-Madison, Madison, WI, United States*, ***Michael Poellmann**, University of Wisconsin, Madison, WI, United States*, ***Seungpyo Hong**, University of Wisconsin-Madison, Madison, WI, United States*

Interactions between programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) are known as an immune ?checkpoint? that exhibits the immune-inhibitory behavior. PD-L1 is commonly expressed on the surfaces of dendritic cells or macrophages, and PD-1 is overexpressed by activated immune cells such as T cells and B cells. In normal conditions, PD-1/PD-L1 interactions restrain regulatory T cells, preventing autoimmunity. However, this interaction mechanism is often hijacked by cancer cells expressing PD-L1, which causes apoptosis of cytotoxic T lymphocytes, suppresses the release of cytokines, and increases immune dysfunction. Thus, inhibition of the PD-1/PD-L1 interactions would be potentially an effective method to destruct tumor cells by restoring the immune responses of antigen-specific T cells. In this study, PD-L1 was targeted because it would be less toxic and would be able to inhibit PD-L1/CD80 interactions as well. Here, we used dendrimers to create multivalent binding effects which can substantially increase overall binding strength and improve effective regulation of signaling processes. We prepared poly(amidoamine) (PAMAM) dendrimers conjugated with PD-L1 antibodies (aPD-L1) using EDC/NHS chemistry. Binding kinetics was then quantitatively measured using surface plasmon resonance (SPR), atomic force microscopy (AFM), and bio-layer interferometry (BLI), revealing that dissociate constants (KD) of the dendrimer-conjugated aPD-L1 to free aPD-L1 were decreased (i.e., more strongly bound) by up to 100-fold (2.6 x 10^-12 vs. 2.5 x 10^-10 M). We are currently testing our hypothesis that this enhanced binding kinetics could be potentially translated into in vitro results. Our study presents a potential strategy to significantly increase the efficiency of immunotherapy using the dendrimer-mediated strong multivalent binding effect.

Liposomal Delivery Of Pathogen-derived Immunogenic Peptides Flags Cancer Cells For Effective Immunotherapy
Student Competition Presentation. NEMB2018-6238

***Nicole Perkins**, University of California, Riverside, Riverside, CA, United States*, ***Shiqun Shao, Zhonghan Li, Siwen Wang**, UC Riverside, Riverside, CA, United States*, ***Michelle Song**, University of California, Riverside, Riverside, CA, United States*, ***Min Xue**, UC Riverside, Riverside, CA, United States*

Genome alteration is a hallmark of cancer, which results in the expression of proteins carrying mutations. In principle, neoantigens containing these mutations could be presented by the cancer cells, which could elicit host immune response. However, cancer cells have developed several strategies to evade the hose immune system. These strategies could effectively modulate the tumor microenvironment to be hostile for T cells and/or down-regulate the immune recognition pathways.

Therapeutics targeting these pathways have recently demonstrated astonishing success and brought new hope to many patients with metastatic cancers that were previously untreatable. Nevertheless, the premise of current immunotherapy approaches largely relies on the recognition of neoantigens and hence the presentation of neoantigens by cancer cells, which is associated with the total mutational burden (TMB) of the cells. Currently, a high TMB has become a criterion for selecting patients for immunotherapy. How to adapt immunotherapy to cancers with low TMB remains an open challenge. Herein, we demonstrate that intracellular delivery of exogenous immunogenic peptides could effectively flag cancer cells for immune response. We delivered an E711-20 peptide derived from Human Papilloma Virus into a human glioblastoma cell line, U87, using fusogenic liposomes. We show that U87 cells can successfully present this peptide through the MHC-I antigen presentation pathway. This presentation can be recognized by HLA-A*0201 restricted antigen-specific CD8 T cells, and elicit immune response. This immuno-flagging process caused significant killing of U87 cells and inhibited the cell proliferation. Generalization of this approach could eliminate the need for endogenous neoantigens and possibly expand the cohort of cancer types that are treatable through immunotherapy, regardless of their TMB status.

TRACK 3
Nano/micro biomechanics and mechanobiology

Track Organizer: **Anna Grosberg**, *University of California, Irvine, Irvine, CA, United States*
Track Co-Organizer: **Mohammad Mofrad**, *Univ of California, Berkeley, Berkeley, CA, United States*

3-2
BIOMECHANICS AND MECHANOBIOLOGY IN ENGINEERED, NATIVE TISSUES, AND EXTRACELLULAR MATRIX
Los Angeles, OMNI Hotel, Crocker Room
10:30am - 11:50am

Session Organizer: **Stephanie Seidlits**, *University of California Los Angeles, Los Angeles, CA, United States*
Session Co-Organizer: **Anna Grosberg**, *University of California, Irvine, Irvine, CA, United States*

Culture Scaffolds with Independently Tunable Biochemical and Mechanical Properties Enable Investigation of Therapeutic Resistance and Invasion in Glioblastoma
Keynote. NEMB2018-6192

Stephanie Seidlits, Weikun Xiao, Alireza Sohrabi, Yasmin Ghochani, Rongyu Zhang, Songping Sun, Harley Kornblum, David Nathanson*, University of California Los Angeles, Los Angeles, CA, United States*

Glioblastoma (GBM) is the most lethal, yet common, cancer originating in the brain. The tumor microenvironment sustains the highly migratory and treatment resistant properties of a sub-population of stem-like cells in GBM (GSCs), which are thought to be largely responsible for tumor recurrence.
Interactions between hyaluronic acid (HA)?a major component of the brain extracellular matrix (ECM) further overexpressed in GBM?and its receptors?including CD44, which is upregulated by GSCs?are reported to facilitate characteristic treatment resistance and aggressive infiltration adjacent to the brain microvasculature. However, the majority of pre-clinical studies do not account for the tumor microenvironment, compromising their clinical relevance. Thus, we have developed HA-based culture platforms that provide a controlled experimental context in which to characterize how the GSC microenvironment facilitates GBM tumor aggression.

Multiple patient-derived GSC lines were cultured in HA-based hydrogels with varied compressive moduli, HA content, and ECM peptides. While GSCs were sensitive to erlotinib, an epithelial growth factor receptor (EGFR) inhibitor, and temozolomide (TMZ), an alkylating chemotherapy, when cultured as gliomaspheres, those in hydrogels mimicking normal brain acquired cytotoxic and cytostatic resistance, which was dependent on HA-CD44 interactions.

GSCs cultured in soft, HA-rich hydrogels increased CD44 expression and EGFR phosphorylation, indicating that HA-bound CD44 and EGFR interacted to facilitate resistance. Notably, resistance kinetics appeared to be dependent on mechanotransduction through HA-bound CD44. In addition, luciferase-encoding reporters for transcription factor activity showed that erlotinib treatment reduced activity of apoptotic factors and increased activity of oncogenic factors. Integrin-binding peptides, such as RGD, provided further protection against drug-induced apoptosis. Migratory activity of GSCs was further enhanced when cultured in hydrogels with peptides derived from integrin-binding sialoprotein, which we have identified to be uniquely upregulated by tumor vasculature, and in those with mechanical properties approximating healthy brain.

In sum, we report biomaterial cultures of patient-derived GSCs in which clinical phenotypes?including 1) kinetics of acquired resistance to multiple therapeutic agents and 2) vasculature-associated infiltration?are preserved. Ultimately, we aim to identify specific GSC-ECM interactions whose targeted disruption represents a viable clinical strategy to prevent and/or delay both therapeutic resistance and vessel-mediated tumor infiltration.

Growth and Differentiation of Neural Stem Cells on Polycaprolactone Microfibers
Technical Presentation. NEMB2018-6170

Nicole Hashemi*, Iowa State University, Ames, IA, United States*

We have fabricated polycaprolactone (PCL) fibers in various sizes and shapes using a microfluidic approach. It was found that the average diameter of the fibers was in the range of 2-37 ?m by varying the flow rates. The microfibers were used to create 3D microenvironments and to study growth and differentiation of adult hippocampal stem/progenitor cells (AHPCs). The results showed that the 3D topography of the PCL substrates, along with chemical guidance cues supported the adhesion, survival, and differentiation of the AHPCs in vitro. It was also found that cells are aligned in the longitudinal direction of fibers. This may prove the efficacy of PCLfibrous scaffolds for cell growth and alignment important in applications such as reconnecting serious nerve injuries and guiding the direction of axon growth.

Implication of species deficiency on fracture toughness in bone
Technical Presentation. NEMB2018-6101

Zubaer Hossain*, University of Delaware, Newark, DE, United States*

Hydroxyapatite (HAP) constitutes the basic building block of bone. It is well known that the intricate hierarchical configuration of a collection of HAP units immersed in a helical mix of collagen fibers governs various nanoscopic mechanical functions of the bone. It also provides a structural basis for various mechanical load carrying capacities under complex combined loading conditions. In spite of the critical role of the HAP unit, the implication of the deficiency of its various chemical elements on overall effective mechanical properties remain less well understood. This presentation will discuss the first-principles results (obtained from a set of density functional theory simulations) on how the effective mechanical properties of a bone are affected by a deficient HAP unit.

A Multiscale Investigation of Substrate Stiffness Influence on Neuronal Cell
Technical Presentation. NEMB2018-6258

Mohan Yasodharababu, Arun Nair*, University of Arkansas, Fayetteville, AR, United States*

Stem cell technologies are the future of regenerative medicine therapies, which has been the major focus of the researchers in the medical and engineering fields. In vitro cell and organ cultures play crucial roles in successfully growing cells or organs for transplantation [1]. Cell cultures often use substrates that mimic the naturally occurring extracellular matrix that support many growing and differentiating cells. Of the matrices that are being developed, the matrigel gained more importance since it yielded better neurons differentiation [2]. There are numerous experimental studies and few models have identified that neuronal cell can also sense the stiffness of underlying substrate [3]. It is observed that increasing the substrate stiffness, it resulted in increase in neurons differentiation. The reason behind this phenomenon is complex, since the mechanosensing events often occurred in multiple spatial and temporal scales [4]. In this study we develop a multiscale computational model which couples molecular interactions at multiple length and time scales. Preliminary results indicate that due to neuron cell contractility and the traction induced in the substrate, the maximum stress is observed on the cortex layer of the neuronal cell. Study is also extended to find the influence of increase in substrate thickness, number of integrin?s and its spatial distribution. These qualitative results will provide the direction for local stiffness influence in the neuronal behavior.

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2. Lv H, Li L, Sun M, et al. Mechanism of regulation of stem cell differentiation by matrix stiffness. Stem Cell Research & Therapy. 2015; 6(1):103.
3. Kothapalli, C. R., & Kamm, R. D. 3D matrix microenvironment for targeted differentiation of embryonic stem cells into neural and glial lineages. Biomaterials. 2013; 34(25), 5995?6007.
4. Shams, H., Soheilypour, M., Peyro, M., Moussavi-Baygi, R., & Mofrad, M. R. K. Looking ?Under the Hood? of Cellular Mechanotransduction with Computational Tools: A Systems Biomechanics Approach across Multiple Scales. ACS Biomaterials Science & Engineering. 2017; 3(11), 2712?2726

TRACK 6
Nanophotonics for biomedical imaging

Track Organizer: **yadong yin**, *University of california riverside, Riverside, CA, United States*
Track Co-Organizer: **peter yingxiao wang**, *UC San Diego, La Jolla, CA, United States*

6-2
MULTIMODALITY IMAGING
Los Angeles, OMNI Hotel, Museum A
10:30am - 11:50am

Session Organizer: **Zhuang Liu**, *Soochow University, Suzhou, Jiangsu, China*
Session Co-Organizer: **Xiaohu Gao**, *University of Washington, Seattle, WA, United States*

Molecular imaging and profiling of cells and clinical specimens
Keynote. NEMB2018-6190

***Xiaohu Gao**, University of Washington, Seattle, WA, United States*

Nanoparticles in the 1-10 nm size range are of considerable current interest, not only because of their unique size-dependent properties but also their dimensional similarities with biological macromolecules (e.g., nucleic acids and proteins). These similarities could allow an integration of nanotechnology and biology, leading to major advances in medical diagnostics, prognostics, and targeted therapeutics. In this talk, I will present recent development of multifunctional nanoparticles for molecular imaging and profiling of single cells and clinical specimens.

Optical Coherence Tomography And Laser Speckle Imaging Of The Brain Though A Transparent Cranial Implant In A Chronic Mouse Model
Student Competition Presentation. NEMB2018-6153

***David Halaney, Carrie Jonak, Nami Davoodzadeh, Junze Liu, Pasha Ehtiyatkar, Hyle Park, Devin Binder, Guillermo Aguilar**, University of California, Riverside, Riverside, CA, United States*

Optical diagnostic and therapeutic neuro-procedures are hindered by the highly scattering cranial bone, necessitating craniotomy (i.e. removal of a section of skull) to provide optical access each time a procedure is performed. Repeated cranial surgeries are expensive and increase risk to the patient. We have proposed a solution to this issue previously by introducing a novel transparent cranial implant made of nanocrystalline yttria-stabilized zirconia (nc-YSZ), which we call the Window to the Brain (WttB) implant. In our previous work, we demonstrated that imaging depth and contrast of optical coherence tomography (OCT) imaging is improved though the WttB implant compared to the native skull in an acute murine model. In this present work, we extend this acute study with OCT performed through the WttB implant immediately following cranioplasty, and at multiple subsequent time points over 30 days in a chronic murine implant model. Additionally, we present complementary laser speckle imaging blood flow mapping across the WttB implant over corresponding time points. Factors influencing the stability of this model such as cranial bone regeneration will be discussed. This work represents the next step towards a viable transparent implant for chronic use, and demonstrates the potential value of this murine implant model as a tool to evaluate the neurological effects of new drugs, procedures, or to study neurological physiology and disease longitudinally over time in a single animal.

Smart Nanoparticles for Imaging and Modulation of Tumor Microenvironment
Keynote. NEMB2018-6193

***Zhuang Liu**, Soochow University, Suzhou, Jiangsu, China*

The tumor microenvironment (TME) is a complex system composed of not only tumor cells but also stromal cells, inflammatory cells, vasculature, and extracellular matrices (ECM). Owing to the insufficient blood flow and hyperpermeable vessels, TME is often characterized by hypoxia, acidity, up-regulated reactive oxygen species (e.g. H2O2), and high interstitial fluid pressures. Those features of TME are known to be closely related to tumor progression and metastases, and in the meanwhile would also lead to the resistances of tumors to various types of treatment methods. In the past several years, our group has developed a number of interesting nanoparticle-based molecular probes to imaging the unique features of TME. For instance, we have fabricated albumin-based nanoparticles for in vivo imaging and semi-quantitative detection of tumor pH, as well as liposome-based nanoprobe for in vivo imaging of H2O2 up-regulated in the tumor, based on in vivo photoacoustic imaging. On the other hand, we have also developed a number of different nanoparticle-based strategies to modulate the TME, particularly tumor hypoxia, so as to realize enhanced cancer treatment. Our next goal is to translate some of our developed techniques into clinical use, although there are still tremendous challenges to be overcome.

TRACK 7
Plenary Speakers

7-3
PLENARY SESSION III
Los Angeles, OMNI Hotel, Bunker Hill Room
2:00pm - 2:50pm

Session Organizer: **John Bischof**, *Univ Of Minnesota, Minneapolis, MN, United States*

Nanomedicine and Genome Editing Approaches for Disease Therapies
Plenary. NEMB2018-6285

***Gang Bao**, Rice University, Houston, TX, United States*

The integration of nanotechnology, biomolecular engineering and biology is expected to produce major breakthroughs in medical diagnostics and therapeutics. In particular, the design, optimization and application of nano-scale probes, carriers and devices will provide unprecedented opportunities for achieving a better control of biological processes, and drastic improvements in disease detection, therapy, and prevention. This talk will highlight the development of nanomedicine and genome editing based stretagies for treating human diseases, including magnetic nanoparticle heating for hyperthermia and nanowarming, nanoparticle-based stem cell targeting, and the use of magnetic force to increase vessel permeability in vivo. I will then discuss the design and optimization of CRISPR/Cas9 systems for treating single-gene disorders such as sickle cell disease, and the importance of reducing or eliminating off-target effects. The opportunities and challenges in developing genome editing based treatment of a wide range of human diseases will be discussed.

TRACK 2
Nano/micro fluidics

Track Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*
Track Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

2-3
LIQUID BIOPSY
Los Angeles, OMNI Hotel, Crocker Room
3:00pm - 4:20pm

Session Organizer: **Fatih Sarioglu**, *Georgia Tech, Atlanta, GA, United States*
Session Co-Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*

Label-Free Isolation of Circulating Tumor Cell Clusters From Whole Blood Using Microfluidics
Keynote. NEMB2018-6252

***Fatih Sarioglu**, Georgia Tech, Atlanta, GA, United States*

Metastasis can result from single cancer cells that acquire a migratory epithelial-to-mesenchymal transition phenotype, and as early as the 1950s, it was also suggested to be mediated by groupings of cells that appear to break off from primary tumors. Such circulating tumor emboli have been reported in both mouse models and human blood specimens, ranging from large thrombi or blood clots carrying tumor cells to clumps of tumor cells mixed with reactive stromal cells. Moreover, intravenously injected tumor cell clusters show higher metastasis initiation capability in the mouse compared to otherwise identical single cells. It is likely that CTC-clusters are less affected from base membrane detachment-induced cell death and shear forces in circulation and hence remain viable to initiate a new tumor. Also, in patients with metastatic cancer, presence of CTC clusters has recently been associated with a poor prognosis. All in all, these findings point to the need to study CTC clusters in detail to understand their role in cancer metastasis as well as their potential clinical utility.

In my talk, I will introduce a microfluidic chip technology to specifically isolate CTC-clusters from unprocessed patient blood. Our technology exploits the unique geometries of cellular aggregates to differentiate CTC clusters from single cells in blood. Specifically, we rely on the strength of cell-cell junctions at physiological flow speed to capture CTC-clusters at bifurcating traps, in which single blood and tumor cells divert to one of the two streamlines and pass through openings designed to allow their passage. This chemistry-free approach enables non-destructive, antigen-independent isolation of CTC-clusters with high sensitivity and purity as well as viable retrieval of CTC-clusters in solution (off the chip) allowing downstream molecular assays. I will describe the design and operation of the device and share results from clinical studies on patients with metastatic melanoma, breast and prostate cancers.

A Microfluidic Platform for Investigation of Physiological Functions of Human Placenta
Technical Presentation. NEMB2018-6172

***Nicole Hashemi**, Iowa State University, Ames, IA, United States*

The human placenta only appears during pregnancy and the function of this organ changes throughout the trimesters of pregnancy. We created a microfluidic device, called a placenta-on-a-chip, to address this issue by using human cells to represent endothelial and syncytiotrophoblast cell layers in the human placenta. Current drug testing methods that are used to test pharmaceutical drugs are considered to be non-responsive for human models. Most of the methods are based on animal models and they have given unreliable results due to differences in the physiological functions of human models and animal models. Therefore, we created a device that can provide more accurate drug testing predictions for placental pharmaceutical drugs. Our placenta-on-a-chip device was created to achieve two main objectives: (a) create a system to mimic the exact physiological function of the human placenta and (b) create a device that can be used to predict fetal risk from pharmacological/social drugs. Human umbilical vein endothelial cells (HUVEC) and trophoblast (BeWo) cells were used to represent the fetal and maternal cells in a human placenta, respectively. Our finalized device will allow us to proceed with drug testing and to understand how the placental barrier works in the human body during pregnancy.

Ultra-sensitive Detection of Circulating Colorectal Cancer Genetic Biomarkers using Integrated Comprehensive Droplet Digital Detection
Student Competition Presentation. NEMB2018-6197

***Tam Vu**, University of California, Irvine, Irvine, CA, United States, **Michael Toledano, Jonathan Chong**, University of California, Irvine Department of Pharmaceutical Sciences, Irvine, CA, United States, **Timothy Abram, Chenyin Ou**, Velox Biosystems, Irvine, CA, United States, **Jan Zimak**, University of California, Irvine Department of Pharmaceutical Sciences, Irvine, CA, United States, **Byron Shen**, Velox Biosystems, Irvine, CA, United States, **Enrico Gratton**, University of California, Irvine Department of Biomedical Engineering, Irvine, CA, United States, **Weian Zhao**, University of California, Irvine, Irvine, CA, United States*

Colorectal cancer (CRC) is the third deadliest cancer worldwide, causing an estimated 774,000 deaths in 2015 (WHO). Even after initial treatment with a combination of targeted radiation, chemotherapy, and/or biologics, patients who achieved remission still face a 30 - 50% chance of relapsing. Monitoring for minimal residual disease (MRD) or cancer relapse has, thus, continued to be a vital component for effective clinical management of colorectal cancer progression and treatment. Current conventional clinical methods (e.g. carcinoembryonic antigen test, histology, and radiological imaging) to monitor cancer recurrence, however, lack the required sensitivity and/or specificity to reliably detect MRD at early stages when treatment is most effective. To address these issues, we present a novel liquid biopsy approach that utilizes a platform technology called Integrated Comprehensive Droplet Digital Detection (IC3D) to detect CRC-specific biomarkers from a sample of blood with unparalleled sensitivity. This approach combines microfluidic droplet partitioning technology, fluorescent multiplexed PCR chemistry, and our own unique and rapid particle counting technology to deliver absolute quantification of ultra-rare genomic targets. Our results demonstrate that the IC3D system can detect oncogenic KRAS G12D mutant alleles against a background of wild-type genomes at a sensitivity of 1 to 10^5 which is 10 to 10^3 more sensitive than existing liquid biopsy platforms such as PCR, qPCR, NGS, and Biorad ddPCR. Therefore, our technology holds the potential to provide clinicians with a powerful decision-making tool to monitor and treat MRD with unprecedented sensitivity for earlier stage intervention.

Vortex-assisted direct multi-molecular delivery into primary cells purified from blood
Technical Presentation. NEMB2018-6121

***Sung-Eun Choi, Srivathsan Kaylan**, Johns Hopkins University, Baltimore, MD, United States, **Mengxing Ouyang**, UCLA, Los Angeles, CA, United States, **Soojung Hur**, Johns Hopkins University, Baltimore, MD, United States*

Recent FDA approval of Kymria, a cell-based gene therapy for pediatric and young adult patients with B-cell precursor acute lymphoblastic leukemia, illustrates that gene therapy can be a life-saving treatment strategy for various complex diseases. Rapid improvement of genomic engineering methods also bolsters the optimism surrounding gene therapy. Genome engineering will not only allow researchers to elucidate the unidentified correlation between genotypes and phenotypes but also possess the superior modularity, specificity, and capability to permanently correct disease-conferring genes. Nonetheless, clinical adoption of genomic engineering technologies is hindered by the low efficiency and high cytotoxicity of gene delivery mechanisms, random off-target effects and impermanent inhibitions of target functions. Efficient multigene delivery methods are also in demand to reduce off-target toxicity by co-expressing therapeutic and protective markers in genetically engineered therapeutic cells. The technique capable of efficient multi-molecule delivery into hard-to-transfect primary cells would expedite the clinical adoption of gene therapies.
We developed an integrated microfluidic electroporator array that is parallelizable and capable of delivering a wide range of molecules, including chemotherapeutic drugs, siRNA, DNA plasmids, miRNA, and intact proteins, into cells purified from heterogeneous cell populations. The system can deliver multiple molecules with precisely and independently controlled dosages in a sequential manner. Various cells were electroporated by applying short-pulsed square waves via micropatterned Au electrodes. Target cells were purified from buffers or diluted whole blood using microscale cell trapping vortices prior to electroporation.
Gentle, yet effective, cell trapping mechanism utilized in the current system not only enables to create cell populations with a uniform size distribution, enhancing the electroporation efficiency but also promotes a uniform cytosolic distribution of transferred molecules.

Moreover, the system provides the real-time monitoring capability for visualization of delivery process of the fluorescent molecules, allowing prompt cell-specific parameter optimizations. Furthermore, superior electroporation efficiency and viability to those of conventional counterparts were achieved when smaller amounts of molecules of interest were administered. Ongoing investigations focus on evaluating the system?s feasibility to perform genome editing of human T-lymphocytes to disrupt T-cell receptor required for the production of allogeneic therapeutic T-cells. The system?s improved performance suggests a great potential to expand the horizons of research and clinical applications where on-chip electroporation technique can be incorporated.

TRACK 5
Nano biosensors for molecular analysis

Track Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*
Track Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

5-2
MICRO/NANOFLUIDICS IN BIOSENSING
Los Angeles, OMNI Hotel, Bradbury Room
3:00pm - 4:20pm

Session Organizer: **Sumita Pennathur**, *UCSB, Santa Barbara, CA, United States*
Session Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

Nanofluidics for bioanalytical systems
Keynote. NEMB2018-6261

***Sumita Pennathur**, UCSB, Santa Barbara, CA, United States*

Electrokinetic flow within nanofluidic systems allows for exquisite measurement and control of analytes. We have previously uncovered mechanisms with which to concentrate, separate, and manipulate individual analytes based on electrokinetic phenomenon. Specifically, the electric double layer - the ion layer that arises based on the surface-fluid interface - interacts with analytes within fluid. Within nanochannels, the effects of the EDL can be sufficient to produce non-intuitive transport behavior. Nanochannels with finite double layers create systems where the conductivity within the nanochannel can be precisely measured. We have used these nanofluidic systems as robust platforms for the study of the behavior of biomolecules under confinement (including the kinetics of proteins and/or DNA). We have thus developed unique bioanalytical devices which use conductivity changes in solution to create cheap, disposable, real-time sensors in a small nanofluidic-based chip. Our latest research aims to translate these research findings to develop not only in vitro diagnostic devices, but also on-body multi-analyte sensors.

An automated droplet-based microfluidic platform for multiplexing biochemical assays in nanoliter volumes
Technical Presentation. NEMB2018-6250

***Diana F Cedillo-Alcantar, Yong Duk Han**, Mayo Clinic, ROCHESTER, MN, United States*, ***Jose Luis Garcia Codero**, CINVESTAV-IPN Monterrey, Apodaca, Nuevo Leon, Mexico*, ***Alexander Revzin**, Mayo Clinic, Rochester, MN, United States*

There is a plethora of robust commercially available ?mix-incubate-detect? assays but multiplexing these assays for small volume analysis is challenging. To address this challenge we are developing a microfluidic system that could be preloaded with biochemical assay reagents and would enable mixing of such reagents with small aliquots of sample. The microfluidic platform includes pneumatic valves which can be automatically controlled via computer interface. To prove the concept of this platform we are carrying out detection of metabolism, cytotoxicity and liver injury markers in samples collected from hepatocyte cultures focusing on glucose, lactate dehydrogenase (LDH) and alanine aminotransferase (ALT).

The microfluidic device operates by controlling the sequence of pneumatic valves opening and closing to allow for solutions to mix. There are 4 to 6 reagent reservoirs each controlled by a microfluidic valve and each capable of mixing with the sample. The reservoir valves are opened sequentially to allow for sample solution to mix with different biochemical assay reagents. Each sample-reagent mixture is then converted into aqueous plugs in nano-liter volume separated by oil phase. Droplet generation happens by on-chip by simply sending the sample-reagent mixture across the intersection with a channel filled with mineral oil.
The enzymatic reaction between target analyte and assay reagent in the droplet produces chromogenic compounds and it induces the color changes of droplet. We quantified the concentration of analytes by measuring the color intensity of droplet. Testing of varying concentrations of glucose (0-10 mM), ALT (0-1000 U/L) and LDH (0-5000 U/L) revealed linear relationship between concentration and color intensity of droplet. In the acquired linear detection ranges, the limit of detection values for glucose, ALT and LDH analyses were respectively calculated as 0.1 mM, 33.2 U/L and 62.6 U/L, based on signal-to-noise characteristics (S/N = 3.3).
We demonstrate that biochemical assays incorporated into microfluidic devices retain sensitivity/limit of detection reported in standard large volume conditions. We are in the process of testing this platform for real-time detection of liver function/injury markers in primary hepatocyte culture.

Mechanically Accelerated Capture of DNA Molecules and Monitoring in Quasi-Real-Time by Robotizing Bio-Photonic-Plasmonic Hybrid Microsensors
Student Competition Presentation. NEMB2018-6110

***Jianhe Guo**, Materials Science and Engieerning, University of Texas At Austin, Austin, TX, United States*, ***Donglei Fan**, The University of Texas At Austin, Austin, TX, United States*

Efficient capture of deoxyribonucleic acid (DNA) on solid surfaces has received immerse research interest for various biotechniques, including DNA extraction, preconcentration, detection, and separation. This work reports an original mechanism to actively accelerate the DNA capture process and significantly reduce the detection time by mechanically rotating bio-photonic-plasmonic hybrid microsensors. The photonic-plasmonic microsensors consist of diatom frustules with surface-coated magnetic thin films and uniformly distributed plasmonic silver (Ag) nanoparticles. The diatom frustules are made of silica with ordered arrays of nanopores offering large surface-to-volume ratio and synergistic-plasmonic resonance for the capture and detection of DNA with surface enhanced Raman spectroscopy (SERS). By manipulating with magnetic tweezers, the photonic-plasmonic microsensors transport and self-assemble in microwells and microfluidic channels, and rotate with tunable speeds for the capture and detection of DNA molecules. Experiments show the capturing rate of DNA can be significantly enhanced to 4 times by controlling the rotation speed of the microsensor to 1200 rpm. At a concentration as low as 80 nM/ml, Raman signals of DNA is obtained 3-time faster than those without rotation. The fundamental mechanism is investigated and attributed to the fluidic boundary layer effect, where the Nernst diffusion layer on the surface of the robotized microsensors is monotonically reduced with flow speed.

Specific power loss demands on magnetic nanoparticles when scaling-up in hyperthermia and nanowarming applications.
Technical Presentation. NEMB2018-6227

***Anirudh Sharma, Hattie Ring, Zhe Gao**, University of Minnesota, Minneapolis, MN, United States*, ***Robert Ivkov**, Johns Hopkins University School of Medicine, Baltimore, MD, United States*, ***John Bischof**, Univ Of Minnesota, Minneapolis, MN, United States*

We provide a detailed analysis of magnetic nanoparticle (MNP) specific loss power (SLP) requirements and performance characterization of different magnetic nanoparticle constructs in the context of two nanomedicine applications ? magnetic hyperthermia-based cancer therapy and magnetic nanowarming of cryopreserved organs. Ideally, both these applications would benefit from a magnetic nanoparticle construct with a high SLP under clinically relevant alternating magnetic field (AMF) conditions. However, the large-scale availability of biocompatible MNPs with low heterogeneity, that meet optimal SLP requirements is limited, due to technical and commercial challenges in large-scale nanomanufacturing. Additionally, scaling-up the AMF system ? power delivered and coil dimensions to accommodate larger specimens, will drive both these technologies towards successful clinical translation. However, scaling up AMF power and coil geometry must take into account the non-uniform power deposition due to eddy currents in large tissues relative to the power deposited by MNPs.

Here, we experimentally evaluate SLPs of various commercial and proprietary MNPs as a function of clinically relevant AMF conditions within two different scaled geometries for AMF systems? (1) A 10 cm long modified solenoid coil with a peak-to-peak axial field upto 100 kA/m at 150 kHz frequency within a 125 ml VOI, capable of treating mice tumors, and nanowarming cryopreserved rat/rabbit organs. (2) A 20 cm long modified Maxwell coil with a peak-to-peak field up to 35 kA/m at 150 kHz within a 2 L VOI, capable of treating rabbit tumors, and nanowarming cryopreserved human organs. We show that hyperthermia based cancer therapy and nanowarming of cryopreserved organs, place different demands on optimal loss power requirements, which depend on (a) biological model ? tumor vs organ (vascularity, physiology, volume, thickness, bioheat transfer) (b) end-points defining clinical efficacy ? tumor destruction vs organ viability (c) constraints/flexibility in the driving AMF conditions ? Atkinson Brezovich criteria, AMF modulation. A comparative analysis of SLP and power deposited due to eddy currents in both coil geometries is performed to elucidate the impact of scaling up AMF systems on non-specific heat deposition.
These results are translated in terms of their clinical relevance in (a) achieving optimal thermal doses in specific cancer models. (b) achieving critical warming rates in nanowarming ? specific tissues and cryoprotective agents. This analysis is then factored in together with biocompatibility and scalability of MNP manufacturing to predict which nanoparticle construct(s) is best suited for clinical translation in each application.

TRACK 6
Nanophotonics for biomedical imaging

Track Organizer: **yadong yin**, *University of california riverside, Riverside, CA, United States*
Track Co-Organizer: **peter yingxiao wang**, *UC San Diego, La Jolla, CA, United States*

6-3
MOLECULAR ENGINEERING OF IMAGING BIOSENSORS
Los Angeles, OMNI Hotel, Museum A
3:00pm - 4:20pm

Session Organizer: **Peter (Yingxiao) Wang**, *University of California, San Diego, La Jolla, CA, United States*
Session Co-Organizer: **Michael Lin**, *Stanford University, Stanford, CA, United States*

Molecular engineering of fluorescent and bioluminescent reporters
Keynote. NEMB2018-6219

***Michael Lin**, Stanford University, Stanford, CA, United States*

Fluorescent proteins are ubiquitous as fluorophores in protein-based sensors of biochemical processes, but are also useful for modulating the photonic output of bioluminescent reporters. Improving the performance of fluorescent proteins could thus benefit numerous reporters for live-cell and live-animal imaging. Using three examples, CyOFP, mCyRFP, and mMaroon, I will discuss how molecular engineering of fluorescent proteins enables new types of reporters of signal transduction in subcellular structures, cell cycle dynamics in cell populations, and gene expression in living animals.

Probing Deep Brain Activity by Ultrafast Near-infrared Light-triggered Release of Biomolecules
Technical Presentation. NEMB2018-6211

***Xiuying Li, Hejian Xiong**, The University of Texas at Dallas, Richardson, TX, United States*, ***Frederik Neuhaus**, University of Fribourg, Fribourg, Switzerland*, ***John Perish, Jonathan Ploski, Sven Kroener**, The University of Texas at Dallas, Richardson, TX, United States*, ***Maria O. Ogunyankin, Jeong E. Shin, Joseph A. Zasadzinski**, University of Minnesota, Minneapolis, MN, United States*, ***Paul Slesinger**, Icahn School of Medicine at Mount Sinai, New York, NY, United States*, ***Andreas Zumbuehl**, University of Fribourg, Fribourg, Switzerland*, ***Zhenpeng Qin**, Univ of Texas At Dallas, Richardson, TX, United States*

Numerous molecules contributes to modulating brain activity and controlling these release of these molecules in deep brain regions remain a significant challenge. For instance, neuropeptides, which function in parallel with classical neurotransmitters, are implicated in cognition, sensorimotor processing and controlling blood flow. Although widely expressed in the brain, studying the effect of endogenously released neuropeptides in vivo has been hampered by inadequate techniques for controlling the release of neuropeptides.
Here we describe our recent studies that use near-infrared tissue-penetrating laser pulses to release or uncage biomolecules from plasmonic gold-coated liposomes, or plasmonic liposomes. We demonstrate that biomolecules can be released rapidly, without heating up the tissue, and with a high degree of control using one- and two-photon stimulation. With this sytem, we show the ability to trigger calcium signaling by intracellular uncaging of inositol triphosphate (IP3), in both an immortalized cell line and primary neurons.

To overcome the limited penetration of light into brain tissue, we investigated gold-coated mechanoresposive vesicles, which consist of liposomes made from the artificial phospholipid that are already under mechanical stress. Near-infrared pulses activate the gold-coating to create nanomechanical stress leading to near-complete vesicle cargo release in sub-seconds. Compared with natural phospholipid liposomes, the photo-release was possible at 40 times lower laser energy and tissue penetration was more than doubled. This allows photo-releasing biomolecules in deep brain tissues in mice.
Work is ongoing to investigate the in vivo photo-release and monitoring of neuropeptides and other neuromodulators. Controlling the release of neuropeptides in real-time in awake animals performing complex behaviors would be transformative, enabling the elucidation of the function of neuropeptides in regulating neural circuits in the brain.
This work was supported by CPRTT (Z. Q.: RP160770) and NSF (Z. Q.:1631910) grants.

Molecular Imaging and Cellular Reprogramming in Immuno-engineering
Technical Presentation. NEMB2018-6256

***peter yingxiao wang**, UC San Diego, La Jolla, CA, United States*

Genetically-encoded biosensors based on fluorescence proteins (FPs) and fluorescence resonance energy transfer (FRET) have enabled the specific targeting and visualization of signaling events in live cells with high spatiotemporal resolutions. Single-molecule FRET biosensors have been successfully developed to monitor the activity of a variety of signaling molecules, including tyrosine/serine/threonine kinases. We have a developed a general high-throughput screening (HTS) method based on directed evolution to develop sensitive and specific FRET biosensors. We have first applied a yeast library and screened for a mutated binding domain for phosphorylated peptide sequence. When this mutated binding domain and the peptide sequence are connected by a linker and then concatenated in between a pair of FRET FPs, a drastic increase in sensitivity can be achieved. It has also been increasingly clear that controlling protein functions using lights and chemical compounds to trigger allosteric conformational changes can be applied to manipulate protein functions and control cellular behaviors4-8. In this work, we first engineered a novel class of machinery molecules which can provide a surveillance of the intracellular space, visualizing the spatiotemporal patterns of molecular events and automatically triggering corresponding molecular actions to guide cellular functions. We have adopted a modular assembly approach to develop these machinery molecules. We engineered such a molecule for the sensing of intracellular tyrosine phosphorylation based on fluorescence resonance energy transfer (FRET) and the consequent activation of a tyrosine phosphatase (PTP) Shp2, which plays a critical and positive role in various pathophysiological processes9-11. We have further integrated this machinery molecule to the ?don?t eat me? CD47 receptor SIRP? on macrophages12-14 such that the engagement of SIRP??and its activation of naturally negative signals will be rewired to turn on the positive Shp2 action to facilitate phagocytosis of red blood cells and target tumor cells, initiated by the specific antigen-targeting antibodies and their interaction with Fc? receptors. Because of the modular design of our engineered molecule, our approach can be extended to perform a broad range of cell-based imaging and immunotherapies, and hence highlight the translational power in bridging the fundamental molecular engineering to clinical medicine. We have also integrated with lights and ultrasound to manipulate the molecular activation of genes and enzymes, which allowed us to control the cellular functions of immunocells with high precision in space and time.

Laser Induced Shockwave Elicits the Transient Mode of the Bimodal Actions of Mechanosensor Piezo1
Technical Presentation. NEMB2018-6278

Yijia Pan, *University of California San Diego, La Jolla, CA, United States*, ***Linda Shi, Daryl Preece, Veronica Gomez-Godinez***, *UCSD, La Jolla, CA, United States*, ***Seung-Hyun Woo***, *Scripps, La Jolla, CA, United States*, ***Shaoying Lu, Shu Chien, Michael Berns***, *UCSD, La Jolla, CA, United States*, ***peter yingxiao wang***, *UC San Diego, La Jolla, CA, United States*

Piezo1 belongs to mechano-activatable cation channels serving as biological pressure sensors. However, the molecular hierarchy downstream of Piezo1 activation remains unclear. In this study, we used biosensors based on fluorescence resonance energy transfer (FRET) to demonstrate that laser-induced shockwaves (LIS) can mechanically activate Piezo1 to induce a transient intracellular calcium (Ca[i]) elevation accompanied by FAK activation. Tuning the degree of Piezo1 activation by chemical stimuli, titrating the dosage of Piezo1 ligand Yoda1 or the level of Piezo1 expression, revealed a bimodal pattern of Piezo1 actions on downstream molecular events. A low degree of Piezo1 activation (transient mode) leads to a transient Ca[i] response with FAK activation, whereas a high degree of Piezo1 activation (sustained mode) causes a sustained Ca[i] response with FAK suppression. These results suggest that the dynamic nature of LIS mechanical stimulation can determine the activation mode of mechanosensor Piezo1 to result in a transient Ca[i] response and a FAK activation.

TRACK 2
Nano/micro fluidics

Track Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*
Track Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

2-4
BIO-INSPIRED SYSTEMS AND SENSORS
Los Angeles, OMNI Hotel, Museum B
4:30pm - 5:50pm

Session Organizer: **Donglei Fan**, *The University of Texas At Austin, Austin, TX, United States*
Session Co-Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*

Plasmonic Active Rotary Nanomotors for Tunable Biochemical Release, Removal, and Microfluidic Manipulation
Keynote. NEMB2018-6236

Donglei Fan, *The University of Texas At Austin, Austin, TX, United States*, ***Jianhe Guo***, *Materials Science and Engieerning, University of Texas At Austin, Austin, TX, United States*

In this talk, we will discuss our recent progress on design, assembling and operation of an innovative type of rotary nanomotors made from micro/nanoscale building blocks, such as nanowires, nanodisks, nanodots, and microrods. Arrays of nanomotors can be efficiently assembled and rotated with controlled angle, chirality and speed to 18,000 rpm, the same level of that of jet engine. The nanomotors are one of the smallest rotary Nanoelectromechanical System (NEMS) Devices, having all dimensions less than 1 µm. They can operate for 80 hours over 1.1 million cycles. The micro/nanomotors are further equipped with plasmonic sensing components. The motorized sensors can readily realize tunable biochemical release and its real time monitoring, enhanced chemical removal, and microfluidic manipulation. This work can inspire a new concept of robotized nanosensors that offer unprecedented precision and control for research in single cell stimulation, cell-cell communication, and system biology.

Preliminary Study of Metal-Oxide-Molecularly Imprinted Polymer (MIP)-based Sensors for Explosive Material
Technical Presentation. NEMB2018-6142

Peng Cheng, *Virginia State University, Midlothian, VA, United States*, ***Godwin Mbagwu***, *Virginia State University, Petersburg, VA, United States*

Environmental pollution are extremely important for human health. Small molecular particles, toxic chemicals, pesticides, or biodegradable substances are often suspended in soil and water and could be harmful to human and aquatic life. Detection of some of these potentially cancer causing agent is a major challenge. As one of the environmental pollutants, 2,4,6-trinitrotoluene (TNT) is not only an explosive material, but also a toxic chemical of a byproduct of explosive manufacture or improper storage. It can be monitored and detected by using proper sensors or devices. In this study, a design, fabrication and testing method of a microfluidic sensor is proposed to detect TNT intensity in water. A microfluidic sensor with a microchannel, some transducers, and a pair of reservoirs is designed and fabricated. A combination of metal-oxide-poly-siloxanes thin film is spin-coated on a substrate. Once explosive materials exist in microfluidic channel, the transducers of the microfluidic sensor detect the resistance changes which are caused by the reaction of the TNT with the thin film nanocomposite. The resistance changes of the transducer then can be recorded and analyzed. This sensing system has the potential of detecting explosive materials and other types of environment contaminants in wet or dry condition. It also has potential applications in food industry, biomedical, chemistry, transportation, aerospace and military fields.

Yeast chemotropism with high spatiotemporal resolution and sensitivity in a biofabricated microfluidic platform
Technical Presentation. NEMB2018-6208

Thanh Vo, John Choy, Xiaolong Luo, *Catholic University of America, Washington, DC, United States*

Chemotropism is an essential response of organisms to external chemical gradients that direct the growth of cells towards the gradient source. This can be seen in the development of the nervous system in which neurons grow towards a target cell, the growth of a pollen tube toward the ovules, and the mating of fungi. Experimental system that brings together a population of mating types A and ? yeast cells and monitors the shmoo formations will be useful to inform on models of chemotropism. To date, few studies have been reported that attempts to reproduce the gradients formed between populations of yeast of opposite mating types. One barrier in performing such experiments is the ability to position populations versus individual yeast cells within proximity of each other without overcrowding, a scenario that the cells physically in contact with each other and prevent gradient formation. This report presents the chemotropic signaling between populations of mating type A and ? yeast cells with spatiotemporal programmability and sensitivity that were revealed with biofabrication in a microfluidic device. Freestanding and semi-permeable chitosan membranes were biofabricated in small apertures (50 µm in all three dimensions) connecting a three-microchannel microfluidic device. Alginate hydrogels were then biofabricated with diffusion of calcium ion through the porous chitosan membranes to posit populations of cells side by side with spatial resolution control in micrometer scale in the middle channel. Medium was then introduced into the two side microchannels and diffused through the porous chitosan membranes into the middle channel to culture the cells. Cells and the mating response were imaged with live-cell microscopy to monitor morphological changes to gain insight into the mating response between populations of cells. The phenotypes of yeast cells because of a mating signal were clearly observed over hours with high spatial resolution and sensitivity. We observed three distinct responses that depended on the distance between A and ? cell populations in the micrometer length scale: the cells either proliferated, developed a stereotypical polarized projection termed a ?shmoo? directed toward the cells of opposite mating type, or polarized growth that appeared random (i.e. not direct toward the source). The observed cell-cell signaling reproduces what occurs in nature and can inform on improving mathematical models of gradient responses. The demonstrated spatial resolution and sensitivity of yeast mating signaling provide insights to further understand how pheromone gradients induce a chemotropic response.

Patterning Multiscale ?Artery-to-Capillary? 3D Vascular Networks in Hydrogels Using LCST Polymers
Technical Presentation. NEMB2018-6108

Jason Wang, Brian O'Grady, John Rector, Shannon Faley, *Vanderbilt University, Nashville, TN, United States*, ***Leon Bellan***, *Vanderbilt University, New York, TN, United States*

A critical challenge currently hindering the production of thick engineered tissue is the need to produce a vascular network of channels throughout the scaffold that can enable exchange of soluble compounds (e.g. nutrients, waste products, gasses) between embedded cells and perfused media. Without such a network, cells embedded deep within the scaffold will die due limited diffusion of these compounds, causing a necrotic core to be formed.

Approaches to overcome this challenge can generally be grouped into ?bottom-up? approaches (which rely on self-assembly of embedded endothelial cells into patent tubule networks) and ?top-down? approaches (which employ patterning techniques such as 3D printing or stereolithography to form perfusable channels within the scaffold). ?Bottom-up? approaches are generally limited to relatively thin scaffolds because, in very thick scaffolds, lumen formation is not fast enough to support perfusion before cells in the center of the scaffold die. The vast majority of patterning approaches, however, are limited to producing channels that are appropriate for mimicking larger vessel (e.g. arteries, arterioles) but are unable to produce capillary-like channel networks (~10 micron diameter). We have developed a patterning approach that uses 3D printed sacrificial templates to form larger channels with well-defined branching geometries, and solvent-spun fibers to form capillary-like channel networks connected to the larger structures. The cell-friendly sacrificial material is the same for both techniques and exhibits LCST behavior with a transition temperature between room temperature and physiological temperature. This allow us to embed the sacrificial template, with complex ?artery-to-capillary? geometry, within a warm gel precursor, and, after the gel has formed, dissolve the sacrificial template simply by cooling to room temperature for a short period of time. We characterize the flow behavior and channel geometries in these complex networks by imaging fluorescent beads injected into the network and compare to the flow desired for various regions of the natural vasculature. By leveraging the complimentary benefits of 3D printing and sacrificial microfiber patterning techniques and using a sacrificial material that disappears with gentle cooling below physiological temperature, we have developed a robust platform for forming complex multiscale channel geometries to support the metabolic demands of functional cells embedded within thick hydrogel scaffolds. We demonstrate that perfused channel networks are necessary to maintain the viability of high densities of metabolically active cells in thick hydrogel scaffolds.

TRACK 5
Nano biosensors for molecular analysis

Track Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*
Track Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

5-3
BIOSENSORS FOR POINT OF CARE TESTING
Los Angeles, OMNI Hotel, Crocker Room
4:30pm - 5:50pm

Session Organizer: **Chenzhong Li**, *Florida International University, Miami, FL, United States*
Session Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

Glucometer Based Nanozyme Integrated Point of Care Biosensors
Keynote. NEMB2018-6280

Chenzhong Li, *Florida International University, Miami, FL, United States*

In recent years, much effort has been devoted toward developing point-of-care (POC) devices. Among them, smart phone enabled paper-based POC devices are a special category due to the advantages of being simple, rapid, on-site, and cost-effective; they have been widely used in home health care and medical testing, even environmental monitoring. The blood glucose meter is one of the most successfully commercialized diagnostic devices on the market because of its low cost, compact size, simple operation, and reliable quantitative results. However, the glucose meters are generally used for only glucose testings. Recently, many groups have reported methods establishing a direct relationship between the concentrations of the targets in the samples and the glucose detected by a glucometer, enabling a number of non-glucose biomarkers to be detected quantitatively.

In this talk, we describe a novel design that combines the traditional lateral flow strip with a commercialized smartphone-enabled glucometer for portable and quantitative detection of a non-glucose target. The concept is demonstrated by using an oxidative DNA damage biomarker, 8-hydroxy-2?-deoxyguanosine (8-OHdG)1. The basic design of the device a colorimetric visual detection platform based on the integration of nanozyme and immunoassay.

The visual detection can provide only qualitative and semiquantitative results. Thus, to enable quantitative analysis, we establish a novel method that transforms the detection of the target to the detection of an nanozyme based converting enzymatic reaction. Considering the inherent advantages of the personal glucose meter, the demonstration of this device, therefore, should provide new opportunities for the monitoring of a wide range of biomarkers and various target analytes in connection with different molecular recognition events.

Electrosprayed thylakoid/graphene oxide composite electrode for harvesting photosynthetic electrons
Technical Presentation. NEMB2018-6148

HyeIn Shin, Hyeonaug Hong, YongJae Kim, WONHYOUNG RYU, *Yonsei University, Seoul, Korea (Republic)*

As a novel renewable and environment-friendly energy conversion system, solar energy conversion using biological resources has been studied recently. Among these, bio-ethanol and microbial fuel cells which convert solar energy by using living resources attract much attention. However, because these systems use plants that are fully grown to produce energy, they go through many energy conversion cycles. In addition, a large part of the solar energy absorbed by the plant is consumed for plant growth, resulting in lower energy efficiency. Therefore, to increase energy conversion efficiency from plant resources, direct extraction of energy directly from the photosynthesis of the plant cells is rigorously investigated. Photosynthesis occurs in the thylakoid membranes of the plant cells, in which photosynthetic electrons (PEs) are generated and transferred with the aid of absorbed photons. To extract photosynthetic electrons (PEs) efficiently, a distance between an electrode and thylakoid membranes need to be as close as possible to enable electrochemical redox reactions. In this work, we employed an electrospraying technique to have uniform and controlled coating of thylakoids on an electrode surface by controlling critical parameters of electrospraying such as substrate movement, feed rate of a thylakoid solution, and the thylakoid concentration. Since the electrode can accept electrons only from the thylakoids directly contacting the electrode, we utilized graphene oxide as connecting material that can transfer PEs between the thylakoid membranes and a main electrode. Optimum conditions for electrospraying the composite solution of thylakoid membranes and graphene oxide were identified, and the resulting PE currents increased up to 4 times than without use of graphene oxide. The concentration ratio of graphene oxide was varied to find conditions for the highest PE currents. It was also confirmed that the PE current did not increase continuously according to electrospraying time. This is likely due to the fact that thicker coating of thylakoids tended to absorb photons before their use for PE production. The photosynthetic current was measured by a three electrode system comprised of a thylakoids coated electrode as a working electrode, a Pt mesh as a counter electrode, and a Ag/Agcl electrode as a reference electrode using a potentiostat.

Microbial Sensing Using Gold Nanoplate-Enhanced Chemiluminescence and Macromolecular Shielding
Student Competition Presentation. NEMB2018-6157

Minh-Phuong Bui, John Brockgreitens, Abdennour Abbas, *University of Minnesota, St. Paul, MN, United States*

Rapid screening and identification of low concentrations of microorganisms in less than 1 hour remains an elusive goal in the fields of medicine, public health and food safety. Although many commercially available techniques are labeled for rapid microbial detection, they often require 24-48 hours of cell enrichment to reach detectable levels. We have recently showed that microorganisms contain disulfide bond-containing proteins in their outer layers that can be cleaved using the reducing agent tris(2-carboxyethyl)phosphine (TCEP) to allow for rapid interactions with spherical gold nanoparticles. Here, we show that TCEP can also act as a powerful oxidant on flat gold nanoplates and subsequently leads to a strong catalysis of luminol chemiluminescence. This catalytic reaction results in up to 100 fold signal enhancement and unprecedented stable luminescence for up to 10 min.
The competitive interaction of TCEP with the gold nanoplates (oxidation) and microorganisms (reduction) is used to introduce a homogenous rapid detection method that allows microbial screening in less than 10 min. Furthermore; we introduce the concept of microbial macromolecular shielding using antibody-conjugated polymers. The combination of TCEP redox activity and macromolecular shielding enables specific microbial identification within 1 hour, with a limit of detection down to 100 cfu.mL-1, without pre-concentration, cell enrichment or heavy equipment other than a portable luminometer. The technique is demonstrated by specific detection of methicillin-resistant Staphylococcus aureus (MRSA) in environmental and urine samples containing a mixture of microorganisms.

The Role of Nanoparticle Design in Determining Analytical Performance of Lateral Flow Immunoassays

Technical Presentation. NEMB2018-6255

Li Zhan, Shuangzhuang Guo*, University of Minnesota, Minneapolis, MN, United States*, ***Fayi Song****, university of toronto, toronto, ON, Canada*, ***Yan Gong****, Xi'an Jiaotong University, Xi'an, Shaanxi, China*, ***Feng Xu****, Xi'An Jiaotong University/China, Shaanxi, China*, ***David Boulware, Michael McAlpine****, university of minnesota, minneapolis, MN, United States*, ***Warren Chan****, university of toronto, toronto, ON, Canada*, ***John Bischof****, Univ Of Minnesota, Minneapolis, MN, United States*

Rapid, simple, and cost-effective diagnostics are needed to improve healthcare at the point of care (POC). However, the most widely used POC diagnostic, the lateral flow immunoassay (LFA), is ?1000-times less sensitive and has a smaller analytical range than laboratory tests, requiring a confirmatory test to establish truly negative results. Here, a rational and systematic strategy is used to design the LFA contrast label (i.e., gold nanoparticles) to improve the analytical sensitivity, analytical detection range, and antigen quantification of LFAs. Specifically, we scaled and modeled the transport and reaction processes in the LFA. We found that the sensitivity greatly depends on the GNP binding process. Our model can predict LFA performance based on nanoparticle design, thus helping to reduce excessive experimentation and more quickly identify and experimentally verify optimum LFA designs. we discovered that the size (30, 60, or 100 nm) of the gold nanoparticles is a main contributor to the LFA analytical performance through both the degree of receptor interaction and the ultimate visual or thermal contrast signals. Using the optimal LFA design, we demonstrated the ability to improve the analytical sensitivity by 256-fold and expand the analytical detection range from 3 log10 to 6 log10 for diagnosing patients with inflammatory conditions by measuring C-reactive protein. This work demonstrates that, with appropriate design of the contrast label, a simple and commonly used diagnostic technology can compete with more expensive state-of-the-art laboratory tests.

TRACK 7
Plenary Speakers

7-4
PLENARY SESSION IV
Los Angeles, OMNI Hotel, Bunker Hill Room 8:00am - 8:50am

Session Organizer: **Guy Genin**, *Washington University in St. Louis, St Louis, MO, United States*

Atomic Force Microscopes for Detecting Molecular Optical Resonances and Tracking and Modifying the Chemistry of Living Cells

Plenary. NEMB2018-6281

Kumar Wickramasinghe,, *University of California, Irvine, CA, United States*

Following an introduction to the Atomic Force Microscope (AFM), In the first half of the talk, we will show that the atomic force microscope can be used to perform nanoscale spectroscopy and microscopy by directly detecting near field optical forces. The photonic force and force gradient modulation on a AFM tip can be translated to a cantilever vibration and detected using the standard AFM optical detection technology. In our experiments we detected electronic resonances of a cluster of a few molecules and recorded their images. The technique has been used to measure and image with both linear and non-linear (stimulated Raman) optical forces. Furthermore, the technique can be used to directly map near field electromagnetic field distributions at nanometer resolution.

In the second half of the talk, we will describe experiments where we have modified SPM probes to create local dielectrophoretic forces and have used these forces to extract and quantify material from living cells. mRNA and micro RNA expression levels within living cells have been quantified as a function of time using this approach. Finally, we have developed an integrated nano-injector that can be used to inject both plasmids and proteins into the cytoplasm or the nucleus of living cells. The combination of the two techniques provide a powerful set of tools that enable us to deterministically modify cells and then measure their response as a consequence of these modifications.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*

Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-5
CIRCULATING TUMOR CELLS AND DRUG DELIVERY
Los Angeles, OMNI Hotel, Museum A
9:00am - 10:20am

Session Organizer: **Milos Marinkovic**, *Biopact, Austin, TX, United States*

Highly Sensitive Detection of Circulating Tumor Cells Based on a Synergistic Effect of Cell Rolling and Multivalent Binding for Monitoring Patient Responses to Radiotherapy

Keynote. NEMB2018-6160

Jiyoon Bu, *University of Wisconsin-Madison, Madison, WI, United States*, ***Ja Hye Myung***, *US Food and Drug Administration (FDA), Silver Spring, MD, United States*, ***Sin-Jung Park***, *University of Wisconsin-Madison, Madison, WI, United States*, ***Michael Poellmann***, *University of Wisconsin, Madison, WI, United States*, ***Michael Eblan, Andrew Wang***, *University of North Carolina, Chapel Hill, Chapel Hill, NC, United States*, ***Seungpyo Hong***, *University of Wisconsin-Madison, Madison, WI, United States*

Circulating tumor cells (CTCs) have attracted a great deal of scientific and clinical interests to be used as multifunctional tumor biomarkers for monitoring therapeutic responses. However, effective detection and isolation of CTCs from human blood still remain a challenge due to the rarity and heterogeneity of CTCs. We previously developed a novel CTC isolation system (CapioCyte) based on a combination of multivalent binding and biomimetic cell rolling, which was shown to significantly enhance sensitivity and specificity of CTC capture. In this study, we aimed to validate the performance of the device using blood samples from cancer patients. We also investigated the clinical significance of CTCs and their kinetic profiles in cancer patients undergoing radiotherapy (RT) treatment.

Patients with histologically confirmed primary carcinoma undergoing RT, with or without chemotherapy, were eligible for enrollment. Peripheral blood was collected prospectively at up to 5 time points, including prior to RT, at the first week, mid-point and final week of treatment, as well as 4 to 12 weeks after completion of RT. CTC capture was accomplished using CapioCyte functionalized with aEpCAM, aHER-2, and aEGFR.

The CapioCyte assay was highly sensitive, enabling detection of CTCs in all 24 cancer patients enrolled and multivalent binding via poly(amidoamine) dendrimers further improved capture sensitivity. We also showed that the use of the cell rolling effect can improve CTC capture specificity (% of captured cells that are CK+/CD45-/DAPI+) up to 38%. Among the 18 patients with sequential CTC measurements, the median CTC count decreased from 113 CTCs/mL before RT to 32 CTCs/mL at completion of RT ($p = 0.001$). CTCs declined throughout RT in patients with complete clinical and/or radiographic response, in contrast to an elevation in CTCs at mid or post-RT in the 2 patients with known pathologic residual disease. In summary, our study demonstrated that multivalent binding and cell rolling can improve the sensitivity and specificity of CTC capture compared to multivalent binding alone, allowing reliable monitoring of CTC changes during and after treatment.

Pyruvate-mediated targeted production of reactive oxygen species in mitochondria to overcome cancer drug resistance

Technical Presentation. NEMB2018-6230

Xiaoming He, *University of Maryland, College Park, MD, United States*

Multidrug resistance is a major challenge to cancer chemotherapy and is a major contributor to cancer relapse after chemotherapy. The multidrug resistance phenotype is associated with the overexpression of the adenosine triphosphate (ATP)-driven transmembrane efflux pumps in cancer cells. We designed a lipid membrane-coated silica-carbon (LSC) hybrid nanoparticle that targets mitochondria through pyruvate, to specifically produce reactive oxygen species (ROS) in mitochondria under near-infrared (NIR) laser irradiation. The ROS can oxidize the NADH into NAD+ in mitochondria, which minimizes the ATP production in mitochondria. This further minimizes the amount of ATP available for the efflux pumps to function. The treatment with LSC nanoparticles and NIR laser irradiation also reduces the expression and increases the intracellular distribution of the efflux pumps. Consequently multidrug resistant cancer cells and their cancer stem cells (CSCs) lose their multidrug resistance capability for at least five days, creating a therapeutic window for chemotherapy. Our in vivo data show that the drug-laden LSC nanoparticles in combination with NIR laser treatment can effectively inhibit the growth of multidrug resistant tumors produced with their CSCs with no evident systemic toxicity.

Hindered transport of nanoparticles and small molecules with convection in ocular drug delivery

Technical Presentation. NEMB2018-6241

Anita Penkova, *University of Southern California, Los Angeles, CA, United States*, ***Satwindar Sadhal***, *Univ Of Southern California, Los Angeles, CA, United States*

High incidence in age-related macular degeneration (AMD), diabetic macular edema (DME), glaucoma and cataract are some of the eye complications which cause irreversible blindness.

This paper demonstrates the hindrance effect on injected mixture of nanoparticles and small molecules (Gd-Nanoparticles and Gd-DTPA) in the middle of the vitreous humor of ex-vivo bovine eye, while active osmotic pumping was created. To create osmotic pumping, we perfused with double saline (1.8%) and at the same time water has been pumped through the vitreous humor. With a forced convection current established, measurements revealed four main effects which accompany intravitreal injected surrogate mixture (nanoparticles and a Gd-DTPA) during perfusion:
1). There is slight movement of the injected Gd-Nanoparticles surrogate. This movement depends on perfusion time.
2). With perfusion, we see different concentration profile in comparison with a control sample (no perfusion).
3). Intravitreal deposition of nanoparticle and small molecule surrogate have shown that the water flow carried the Gd-DTPA farther than the nanoparticles, even though the two solutes, being mixed, were subjected to the same convective flow conditions.
4). From our development of the convection based model, these findings lead to an adjustment to the conventional modeling of convection transport by introducing a filtration coefficient to the classical equation.
The long-term plan is to obtain quantitative data on the hindrance and propose predictive numerical model of the convective transport in the vitreous humor in regards to profile concentration distribution with and without control perfusion. Thus, obtaining property values for numerical input (porosity data, intravitreal flow rate) and knowing how increased flow rate influences surrogate transport in both aspects directionally in terms of convective current and diffusion characteristics will give better ideas in the design of medication for glaucoma treatment based on nanoparticle and small molecule size.

Formulation and Recovery of Fast-acting Lumefantrine Nanoparticles for Oral Malaria Therapy

Technical Presentation. NEMB2018-6268

Jie Feng, Yingyue Zhang, Simon A. McManus, Robert K. Prud'homme*, Princeton University, Princeton, NJ, United States*

Malaria is a major source of mortality in developing tropical regions and new low-cost therapies are needed. Lumefantrine is a Biopharmaceutics Classification System class II drug, and increasing the bioavailability of lumefantrine has the potential to reduce the dose and number of required administrations per treatment, thus reducing the financial burden of malaria therapy. Formulating therapeutics into nanoparticles can increase their bioavailability by reducing drug crystallinity and increasing surface area, thereby resulting in faster dissolution kinetics. In this study, we use Flash Nanoprecipitation to encapsulate lumefantrine into nanoparticles with low-cost stabilizers (zein/casein, HPMCAS, and lecithin) and assess the release of lumefantrine in simulated gastric and intestinal fluids. For the low-melting-point lumefantrine, a feasible spray-drying protocol was further developed to dry lumefantrine-encapsulated nanoparticles into powders, while maintaining the physical state of the drugs. In particular, the effect of the drying temperature on the crystallinity and release profile of lumefantrine was investigated by X-ray differaction, differential scanning calorimetry and in-vitro release experiments. The release experiments show that lumefantrine formulations with all stabilizers showed superior dissolution compared to crystalline lumefantrine release in simulated fasted and fed intestinal media. Remarkably, particles synthesized with zein/casein and HPMC exhibited near complete release in under one hour. These cheap and efficient formulations have great potential to be developed into future therapies for malaria, and the results also highlight the potential of combining Flash Nanoprecipitation and spray-drying as a feasible and versatile platform to design and rapidly recover amorphous nanoparticles in a solid dosage form.

TRACK 3
Nano/micro biomechanics and mechanobiology

Track Organizer: **Anna Grosberg***, University of California, Irvine, Irvine, CA, United States*
Track Co-Organizer: **Mohammad Mofrad***, Univ of California, Berkeley, Berkeley, CA, United States*

3-3
BIOMECHANICS OF THE NUCLEUS
Los Angeles, OMNI Hotel, Museum B
9:00am - 10:20am

Session Organizer: **Kris Dahl***, Carnegie Mellon University, Pittsburgh, PA, United States*
Session Co-Organizer: **Soham Ghosh***, University of Colorado Boulder, Boulder, CO, United States*

Mechanical properties of the cell nucleus with implications in development, disease and aging

Keynote. NEMB2018-6251

Kris Dahl*, Carnegie Mellon University, Pittsburgh, PA, United States*

The sequencing of the human genome has provided a wealth of scientific information, but this information is limited by the poor understanding of the mechanisms which control gene expression. In addition to containing the code for the cell, the genome within the nucleus is a complex, self-assembled polymeric structure with unique rheological properties. The genome of metazoan cells is surrounded by an intermediate filament network known as the nucleoskeleton. Using spectrocopy, imaging, micromanipulation and computational techniques, we measure the mechanics of the nucleoskeleton and the nuclear interior at various length scales. We are particularly interested in the role that force and cytokine treatment play in altering nuclear mechanics and gene expression in primary human cells. Motor activity from the cytoskeleton transduced through the nucleoskeleton impacts the driving force for nuclear and subnuclear movement, and altered chromatin condensation shifts the resistance and propagation of forces. We also quantify nuclear stiffness in a broad spectrum of cell types: cells with less regulated gene expression patterns, including stem cells and cancer cells, have much softer nuclei whereas aged cells have stiffer nuclei. While the mechanisms directing stiffness are still being elucidated, we have quantified dramatic downstream impacts of nuclear stiffness on cellular migration. Generally, nuclear architecture and mechanics impacts cell fate directly by altering cell stiffness and indirectly by modulating gene expression. These results have broad implications in cell biology, inhibition of cancer metastasis, and for applications in cellular therapies.

Predicting Individual Cardiomyocyte Fiber Organization In Spatially Constrained Cells

Poster Presentation. NEMB2018-6145

William Sherman, Anna Grosberg*, University of California, Irvine, Irvine, CA, United States*

A functional, healthy heart relies on the synchronized contractions of cells within the laminar sheets in order to pump blood throughout the body. However, structural changes in the heart at the millimeter and centimeter scale result in dramatic changes to individual cardiomyoctes at the micrometer scale. To understand heart disease or to engineer heart tissue, it is important to be able to predict how this structural remodeling affects the internal mechanisms of the individual cells. Current predictive models for whole cardiomyocyte myofibrilogenesis have not included the placement of the nucleus and have been unable to construct continuous actin fiber networks. Consequently, this limits their predictive power in cells where fibers can be seen acting as continuous bending curves, particularly around the nucleus.

Including spatial scales allows for the exploration of a larger range of cell sizes and shapes than previous models. For each simulated cell, various potential fiber networks can be constructed that are energetically favorable to the cell and take into account both individual myofibril bending and placement constraints due to spatial factors. Furthermore, nucleus placement has been included so that its influence on the resulting myofibril distribution can be examined.

By incorporating scaling terms into the Grosberg et al. model of myofibrillogenesis, it is possible to construct fiber networks by minimizing the simulated cell?s free energy. This energy function considers both the energetic cost of building and placing a fiber with only fibers that reduce the system?s total energy being designated for placement. The validity of each portion of the model has been tested using limiting cases and by comparing the model outputs to experimentally consistent data. By utilizing the interplay between individual myofibril bending energy and cellular membrane deformation energy, fiber networks can be constructed that mimic the actin network seen in experimental data by attempting to optimize the cell?s free energy.

By rescaling previously fitted parameters and building upon preceding results, it is possible to explore a variety of dynamic relationships. One such relationship is how the focal adhesion dynamics for different sized cells and the placement of the nucleus influences the proposed actin network. Since previous models were not designed to explore these types of relations, this reformulation gives new insights into how the internal architecture of different sized cells is influenced by the coordination across multiple length scales. Further exploration can focus on the link between fiber dynamics and z-line registration in adjacent myofibrils.

Image Texture-Based Elastography of the Intranuclear Space
Technical Presentation. NEMB2018-6237

Soham Ghosh, Benjamin Seelbinder, *University of Colorado Boulder, Boulder, CO, United States*, ***Victor Crespo Cuevas***, *Universitat Politecnica de Catalunya, Barcelona, Spain*, ***Corey P. Neu***, *University of Colorado Boulder, Boulder, CO, United States*

The cell nucleus is known to contain, maintain, and interpret the genomic information. The chromatin in the nucleus is a highly organized structure that organizes for efficient DNA replication and transcription. The heterochromatin is a compact region with high DNA density, while the euchromatin is a less compacted region that is believed to contain most transcriptionally-active genes. The relative mechanical role of the euchromatin and heterochromatin regions can reveal the mechanobiological function of the chromatin. However, intranuclear mechanics (e.g. stiffness of subnuclear domains) is not well understood, in part due to technical challenges of measurement inside the subcellular organelle. We propose a noninvasive image texture-based elastography technique that can elucidate relative stiffness of euchromatin and heterochromatin regions.

Cardiomyocytes (CM) were derived from embryonic H2b-eGFP mice and were seeded on two groups of silicon substrates with soft (15 kPa) and stiff (400 kPa) elastic properties to mimic normal and fibrotic cardiac environments. The histone tag present in all nucleosome complexes rendered the image texture. During spontaneous CM beating, the deforming nuclei were imaged using an epifluorescenece microscope. Further, deformation microscopy, a technique developed in our lab, was applied to the reference undeformed and deformed images to quantify the spatial intranuclear displacement map. The technique relies on image texture and registers a warped undeformed image template to images of the deformed nucleus. We further segmented and defined euchromatin and heterochromatin regions of interest that were assumed to have uniform stiffness. We solved an inverse problem to quantify the relative stiffness of the two intranuclear regions, with known displacements defined as boundary conditions, and minimization of nodal displacements obtained from finite element forward simulation and the deformation microscopy. A linear elastic material model was used to calculate the Young?s Modulus with known Poison?s ratio 0.35. Known forward simulations were used to validate the technique and to quantify the sensitivity to noise.

Initial studies indicate that for CM cultured on soft substrates that match their native environment, the ratio of heterochromatin to euchromatin stiffness was ~10, while for stiff substrates, the ratio was ~0.05. The reversal of the stiffness in the intranuclear domains is most likely caused by the altered mechanobiological response through mechanisms that need further studies. The reported technique can be applied to broader application areas on any images that have inherent texture with an assumption that the image intensity is a function of the stiffness.

The effect of heart mechanics on cells with the Lamin A/C mutation and its relation to heart disease
Technical Presentation. NEMB2018-6132

Richard Tran, *University of California, Irvine, Ontario, CA, United States*, ***Alex Ochs, Linda McCarthy, Cecilia Nguyen, Mark Siemens, Michael Zaragoza***, *UCI, Irvine, CA, United States*, ***Anna Grosberg***, *University of California, Irvine, Irvine, CA, United States*

Although mutations in the Lamin A/C (LMNA) gene can cause a variety of devastating diseases, the disease mechanisms are still unknown. Lamin A and C proteins play a crucial role in forming a meshwork under the nuclear membrane, providing the nucleus with mechanical integrity as well as interacting with other proteins for gene regulation. In this study, we have identified three unique families with variations of the LMNA mutation, which primarily results in the phenotype of heart disease. Despite having a LMNA mutation, these patients do not have symptoms like that in Hutchinson-Gilford progeria syndrome or Emery-Dreifuss muscular dystrophy where areas affected are more general like the skin and all muscles. It is a mystery why a mutation to the protein in every nucleus of the body in the case of these families manifests as a disease of only the heart. We hypothesized that the cyclic strain cardiomyocytes are constantly exposed to within the heart is an important factor that differentiates heart cells from others in the body. Thus, we predicted that non-contracting cells from these patients will be indistinguishable from cells originating from control populations unless they have undergone cyclic stretch. In order to test this, a stretcher device was used to induce cyclic strain upon cells with and without the LMNA mutation. After culturing both static and stretch conditions in parallel, the cells were fixed, immunostained, imaged, and analyzed to collect variables such as nuclei defectiveness, nuclear eccentricity, and nuclear area. Preliminary results indicate a difference in the phenotype presented by stretched cells from individuals with and without the LMNA mutation. For example, stretching generally causes increased eccentricity of the nuclei, but elongation was found to be greater in both stretch and static conditions for cells with the LMNA mutation when compared to those without. Such changes to nuclear shape could be playing a role in gene expression regulation. Thus, there is a possibility that the unique mechanical environment of the heart affects cells with the LMNA mutation differently from those in the rest of the body.

TRACK 4
Nanomanufacturing and functionalization of biomaterials

Track Organizer: **Song Li**, *University of California, Los Angeles, Los Angeles, CA, United States*
Track Co-Organizer: **Hyunjoon Kong**, *University of Illinois At Urbana-Champaign, Champaign, IL, United States*

4-1
MICROFLUIDICS AND SOFT MATERIALS FOR BIOLOGY AND MEDICINE
Los Angeles, OMNI Hotel, Hershey Room
9:00am - 10:20am

Session Organizer: **Noo Li Jeon**, *Seoul University, SEOUL, Korea (Republic)*
Session Co-Organizer: **Yuhang Hu**, *University of Illinois At Urbana-Champaign, Urbana, IL, United States*

Bio-inspired adaptive fluid-infused porous film with tunable wettability and bio-adhesion
Keynote. NEMB2018-6260

Yuhang Hu, Inkyu Oh, *University of Illinois At Urbana-Champaign, Urbana, IL, United States*

Materials that adapt dynamically to environmental changes are currently limited to two-state switching of single properties, and only a small number of strategies that may lead to materials with continuously adjustable characteristics have been reported. Here we introduce adaptive surfaces made of a liquid film supported by a nanoporous elastic substrate. As the substrate deforms, the liquid flows within the pores, causing the smooth and defect-free surface to roughen through a continuous range of topographies. We show that a graded mechanical stimulus can be directly translated into finely tuned, dynamic adjustments of wettability. In particular, we demonstrate its ability to continuously manipulate liquid droplets from free sliding to completely pinned and to mixing and jetting. We also demonstrate tunable bio-adhesion using the new dynamic adaptive surface. This strategy should make possible the rational design of tunable, multifunctional adaptive materials for a broad range of applications.

A Molecular Dynamics Study Of Self-Assembly And Stability Of Synthetic Collagen Molecules For Tissue Engineering Applications.
Student Competition Presentation. NEMB2018-6151

***Atul Rawal, Kristen L Rhinehardt, Ram V Mohan**, Joint School of Nanoscience & Nanoengineering, GREENSBORO, NC, United States*

Collagen is a pervasive, extracellular matrix (ECM) protein. From skin and bones to blood vessel and lungs, it is found all over the human body. Even tough natural collagen has been a template for tissue engineering and various other applications, extraction from natural sources is time consuming and sometimes costly. It is also difficult to render and can also prompt undesired biological and pathogenic changes. Synthetic collagen, manufactured from nanomaterials, has shown to mimic the unique properties that are present in natural collagen molecules. However, these properties have been noted to be affected by their surrounding environments as well as various solvents. In this study, synthetic collagen is investigated for the development of a novel bio-material, via self-assembly, to fabricate ECM mimicking scaffolds for tissue engineering. We focus the study to mimic the properties of natural collagen in synthetic peptide collagen molecules with lengths of less than 10 nanometers, for the manufacturing of a composite polymeric collagen blend of two synthetic collagen molecules. Molecular dynamics modeling of two different synthetic collagen molecules are performed to investigate the intramolecular and intermolecular interactions responsible for various properties of collagen, including self-assembly and stability. Simulations of both single collagen molecule, and multiple collagen molecules are investigated to study the intermolecular interactions. An average calculated distance of approximately 2 angstroms between the molecules was found to correspond with self-assembly process of the fibrils. Similar binding behavior is observed between both collagen molecules, with the hydrogen bond between Glycine15?Alanine43 residues being the most repetitive bond, indicating its importance in collagen self-assembly.

96-Well Format 3D Microfluidic Platform for Vascularized Micro Physiological System Applications

Keynote. NEMB2018-6288

***Noo Li Jeon**, Seoul University, SEOUL, Korea (Republic)*

Polydimethylsiloxane (PDMS) has been widely used in fabricating microfluidic devices for prototyping and proof-of-concept experiments. Due to several material limitations, PDMS has not been widely adopted for commercial applications that require large-scale production. This presentation will describe a novel Injection-Molded Plastic Array 3D Culture (IMPACT) platform that incorporates microfluidic design to integrate patterned 3D cell culture within a single 96-well (diameter = 9 mm).Cell containing gels can be sequentially patterned by capillary-guided flow along the corner and narrow gaps designed within the 96-well form factor. Compared to PDMS-based hydrophobic burst valve designs, this work utilizes hydrophilic liquid guides to obtain rapid and reproducible patterned gels for co-cultures. When a liquid droplet (i.e. cell containing fibrin or collagen gel) is placed on any part of the corner, spontaneous patterning is achieved within 1 second. Optimal dimensionless parameters required for successful capillary loading have been determined. To demonstrate the utility of the platform for 3D co-culture, angiogenesis experiments were performed by patterning HUVEC (human umbilical endothelial cells) and LF (lung fibroblasts) embedded in 3D fibrin gels. The angiogenic sprouts (with open lumen with tip cells expressing junctional proteins) are comparable to those observed in PDMS based devices. The IMPACT device has the potential to provide a robust high-throughput experimental platform for vascularized microphysiological systems.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-6
MICROFLUIDICS AND EXOSOMES FOR DISEASE DETECTION
Los Angeles, OMNI Hotel, Bradbury Room 10:30am - 11:50am

Session Organizer: **Ying Li**, *University of Connecticut, Storrs, CT, United States*

Microfluidic Technologies for the Isolation and Characterization of Exosomes for Disease Detection and Evaluation of their Role in Progression

Keynote. NEMB2018-6248

***Sunitha Nagrath**, University of Michigan, Ann Arbor, MI, United States*

Exosomes are nanovesicles, approximately 50-200nm in diameter, that are released into the blood stream through exocytosis. After excretion, exosomes are uptaken by distant cells, allowing for cell-cell communication and the transfer of cellular information. Exosomes contain proteins, miRNA, mRNA, and DNA fragments, allowing the transfer of information from parent cell to distant cells. Several groups have determined specific miRNA and protein compositions in exosomes that have potential as diagnostic markers. Developing an assay for early detection or monitoring of disease from exosomal information would increase the clinical reach of an assay, allowing for easy shipment to a central lab outside the hospital if necessary. The development of such a diagnostic tool first calls for the development of an assay? Toolbox? That can interrogate exosomes for mRNA, miRNA, proteins, and even DNA fragments. Here we present microfluidic technologies for the reliable isolation and the characterization to discover their role in cancer and neurological disease.

Dendrimer-mediated exosome surface capture and characterization of multivalent binding by AFM force spectroscopy.

Student Competition Presentation. NEMB2018-6159

***Michael Poellmann**, University of Wisconsin, Madison, WI, United States*, ***Ashita Nair, Seungpyo Hong**, University of Wisconsin-Madison, Madison, WI, United States*

Cancer cells shed nanoscale vesicles called exosomes that contain genetic moieties such as RNA and characteristic proteins that reflect the state of the parent tumor. Circulating exosomes have thus been considered a promising biomarker that can provide both diagnostic and prognostic information of cancer status via liquid biopsy. However, the isolation of exosomes in quantities sufficient for biopsy is exceptionally challenging due to their small size and buoyancy. In this work, we have developed a novel exosome capture surface that is engineered to support multivalent binding at the nanoscale. The hyperbranched structure of partially-carboxylated, poly (amidoamine) (PAMAM) dendrimer nanoparticles supported an exceptionally high density of capture antibodies in a very small area, while the flexible nature of the polymer supported multivalent interactions. Exosome capture from conditioned media and human serum was demonstrated by ELISA and RNA assays.

Experiments showed that highest capture efficiency was obtained with two layers of PAMAM tethered by poly(ethylene glycol) (PEG) linkers and functionalized with partially-reduced antibodies. Ultimately, functionalization of fiberglass filters provided enough surface area to capture 10 ng RNA per mL of healthy human serum, a quantity sufficient for downstream analysis. Next, we used an atomic force microscope (AFM) to show that the enhanced capture sensitivity of PAMAM surfaces was due to multivalent binding and additional nonspecific interactions between the polymer coating and a functionalized, nanoscale probe. We observed a mean of 2.9 discrete antibody unbinding events when separating the probe from PAMAM surfaces compared to 1.6 on PEG controls. The total work required to separate the probe from PAMAM surfaces was 1980 pN nm compared to 710 pN nm for functionalized PEG. We additionally observed significantly greater work in separating the probe from non-functionalized PAMAM compared to PEG, indicating that electrostatic, van der Waals, or other nonspecific interactions contribute to exosome capture by partially-carboxylated PAMAM. The results show the promise of PAMAM surfaces in highly sensitive and specific liquid biopsy applications.

Opening the blood-brain barrier using high-frequency pulsed electric fields in a microfluidic model of the blood-brain barrier

Student Competition Presentation. NEMB2018-6231

Philip Graybill*, Virginia Tech, Blacksburg, VA, United States*, ***Mohammad Bonakdar****, Helbling Precision Engineering, Cambridge, VA, United States*, ***Rafael Davalos****, Virginia Tech, Blacksburg, VA, United States*

Methods of opening the blood-brain barrier (BBB) are critical because of their potential for treating many neurological disorders and diseases. The BBB creates a significant blockade to drug delivery by strictly regulating the transfer of substances from the blood to the brain tissue. Electrical energy in the form of high-energy pulses may provide a minimally invasive focal technique to open the BBB. High-frequency pulsed electric fields, such as those used for tumor ablation in high-frequency irreversible electroporation (H-FIRE), may allow for controlled opening of the BBB under certain pulsing parameters. In this study, we investigate the effect of high-frequency pulsed electric fields on the BBB using an in vitro microfluidic BBB model. We measured BBB permeability in real-time by optically monitoring the diffusion of a fluorescent dye (fluorescein) across a monolayer of human cerebral microcapillary endothelial cells (hCMECs). A simple microfluidic geometry allowed us to test six electric field magnitudes spanning a three-fold range against a control group during a single experiment. We found reversible opening and irreversible opening (cell death) depending on electric field magnitude and pulse number. Transient BBB disruption to fluorescein (376 Da) occurred within the first hour after pulsing and reached a maximum approximately 15-30 minutes after pulsing. Preliminary results indicate significant electrofusion above ~1000V/cm and no significant disruption occurs below ~300V/cm. Our results provide an important foundation for planning treatments to maximize BBB disruption for drug transport while maintaining a high degree of cell viability.

High-Temporal-Resolution Measurements of Polymer Micellization Kinetics by Integrating a Microfluidic Device with Synchrotron X-ray

Student Competition Presentation. NEMB2018-6234

Chang Liu, Joseph Kalkowski, Paola León-Plata, Magdalena Szymusiak, Pin Zhang*, University of Illinois at Chicago, Chicago, IL, United States*, ***Thomas Irving, Weifeng Shang****, Illinois Institute of Tehcnology, Chicago, IL, United States*, ***Sagar Kathuria, Osman Bilsel****, University of Massachusetts Medical School, Worchester, MA, United States*, ***Ying Liu****, UNIVERSITY OF ILLINOIS AT CHICAGO, CHICAGO, IL, United States*

Block copolymers have been extensively investigated as drug carriers for a wide variety of ingredients such as small molecules, proteins, and genetic materials. However, one major hurdle that prevents block copolymer-based nanomedicine from hitting the market is insufficient control and poor reproducibility on particle properties in scale-up procedures, including size, morphology, and surface properties. Therefore, a complete understanding on the kinetics of the block copolymer micelle growth is necessary to fully control the self-assembly process during particle formation and to maintain the stability of the structures.

In this study, we realized the in situ micellization kinetics measurements of an amphiphilic diblock copolymer, poly (ethylene-glycol)-b-poly (caprolactone) (PEG-b-PCL), with micrometer spatial and millisecond temporal resolutions using synchrotron x-ray scattering integrated with a microfluidic device. Micellization of the diblock copolymer was initiated in the microfluidic device by solvent exchange. Evolutionary states of the nanostructures were detected by small-angle X-ray scattering at thirty different positions along the flow direction, which was translated into time intervals. For the first time, three stages of polymer micellization ? Nucleation, merging, and insertion, were observed. Understanding the kinetics of nanoparticle formation will provide important guidance, which is not available currently, for designing and optimizing nanostructures with a wide spectrum of applications.

TRACK 3
Nano/micro biomechanics and mechanobiology

Track Organizer: **Anna Grosberg**, *University of California, Irvine, Irvine, CA, United States*
Track Co-Organizer: **Mohammad Mofrad**, *Univ of California, Berkeley, Berkeley, CA, United States*

3-4
COMPUTATION AND MODELING IN BIOMECHANICS AND MECHANOBIOLOGY
Los Angeles, OMNI Hotel, Crocker Room
10:30am - 11:50am

Session Organizer: **Taiji Adachi**, *Kyoto University, Kyoto, Japan*
Session Co-Organizer: **Anna Grosberg**, *University of California, Irvine, Irvine, CA, United States*

Force Feedback in Multicellular Morphogenesis from Molecule to Tissue: In vitro and in silico Studies

Keynote. NEMB2018-6119

Taiji Adachi*, Kyoto University, Kyoto, Japan*

Mechanical forces play important roles in living tissues and organs to determine their functional shape and structure. In this study, we investigated how locally generated mechanical forces and their feedback result in the macroscopic regulation of multicellular tissue/organ morphogenesis, and how such multiscale approach based on modeling and simulation allows us to explore the roles of mechanical force feedback in determining the tissue/organ-level functional shapes.

In multicellular morphogenesis, tissue folding is controlled by local internal mechanical forces such as tensile (contractile) forces generated in actin-myosin networks and compressive (pushing) forces due to tissue volumetric increase by cell division and proliferation. Mechanical forces at the adherens junctions are sensed at the microscopic molecular level by mechanosensory protein alpha-catenin, and integrated to determine the macroscopic tissue morphology through multiscale interactions. To better understand such complex multiscale phenomena, mathematical modeling and computer simulation based on mechanics will give us a powerful framework for conducting in silico experiments by combining with in vitro experiments.

A Minimal model of Fractional Order for Human Respiratory Impedance

Technical Presentation. NEMB2018-6218

Bharat Soni, Ameeya kumar Nayak*, Indian Institute of Technology Roorkee, Roorkee, Uttarakhand, India*

In this paper we are purposing an equivalent fractional order electrical model with 3 lumped parameters: resistance (R), compliance (C) and inertance (I), to study the lung aerodynamics. This model involves the solution of Navier Stokes equation for axisymmetric airways. The electrical analogy for viscoelastic lung tissues is considered to detect the changes in lumped parameters (impedance) for healthy and diseased airways. The impedance values are obtained for clinical frequency range 4-48 Hz. The collected data is considered for the computation of breathing under spontaneous ventilation effect which can provide the nature of the flow to be laminar in most of the airway generations. By using Kalman filter approach, we are obtaining optimal values of parameters to formulate the fractional order model. This model can further help us in identifying the effects of diseases in lung morphology.

Keywords: human respiratory system, lung impedance, modeling, fractional order model, Kalman filter approach.

A macro-micro modeling approach to determine in-situ heart valve interstitial cell contractile behaviors in native and synthetic environments

Technical Presentation. NEMB2018-6242

Michael Sacks*, The University of Texas At Austin, Austin, TX, United States*

Mechanical forces are known to regulate valve interstitial cell (VIC) functional state by modulating their biosynthetic activity, translating to differences in tissue composition and structure, and potentially leading to valve dysfunction. VICs can change phenotype dynamically; in diseased valves VICs switch to a myofibroblast-like phenotype and become contractile. Activated VICs display prominent SMA stress fibers and an increase in ECM remodeling. Yet, while advances have been made toward the understanding of VIC behavior ex-situ, the VIC biomechanical state in its native extracellular matrix (ECM) remains largely unknown. We hypothesize that improved descriptions of VIC biomechanical state in-situ, obtained using a macro-micro modeling approach, will provide deeper insight into AVIC interactions with the surrounding ECM, revealing important changes resulting from pathological state, and possibly informing pharmaceutical therapies. To achieve this, a novel integrated numerical-experimental framework to estimate VIC mechanobiological state in-situ was developed. Flexural deformation of intact valve leaflets was used to quantify the effects of VIC stiffness and contraction at the tissue level. In addition to being a relevant deformation mode of the cardiac cycle, flexure is highly sensitive to layer-specific changes in VIC biomechanics. As a first step, a tissue-level bilayer model that accurately captures the bidirectional flexural response of AV intact layers was developed. Next, tissue micromorphology was incorporated in a macro-micro scale framework to simulate layer-specific VIC-ECM interactions. The macro-micro AV model enabled the estimation of changes in effective VIC stiffness and contraction in-situ that are otherwise grossly inaccessible through experimental approaches alone. While the use of native tissues provided much insight, we also utilized 3-D hydrogel encapsulation, which is an increasingly popular technique for studying VICs. Specifically, we employed poly(ethylene glycol) (PEG) gels to encapsulate VICs and study their mechanical response to the surrounding hydrogel stiffness and to varying levels of adhesion availability. Cell contraction was elicited through chemical treatments and the resulting mechanical properties of the constructs were measured through end-loading flexural deformation testing. We applied the downscale model, which was improved by 3D stress fiber visualization. The resulting cell force levels were comparable to native in-situ results. Overall, the developed numerical-experimental methodology can be used to obtain VIC properties in-situ. Most importantly, this approach can lead to further understanding of AVIC-ECM mechanical coupling at in receptor level under various pathophysiological conditions and the investigation of possible treatment strategies targeting the myofibroblast phenotype characteristic of early signs of valvular disease.

TRACK 4
Nanomanufacturing and functionalization of biomaterials

Track Organizer: **Song Li**, *University of California, Los Angeles, Los Angeles, CA, United States*
Track Co-Organizer: **Hyunjoon Kong**, *University of Illinois At Urbana-Champaign, Champaign, IL, United States*

4-2
NANOELECTRONICS FOR BIOLOGICAL MONITORING
Los Angeles, OMNI Hotel, Museum A
10:30am - 11:50am

Session Organizer: **Kwan Hyi Lee**, *Korea Institute of Science and Technology (KIST), Seoul, Korea (Republic)*
Session Co-Organizer: **Hyunjoon Kong**, *University of Illinois At Urbana-Champaign, Champaign, IL, United States*

Nanodevice-based monitoring for clinical translational research
Keynote. NEMB2018-6267

***Kwan Hyi Lee**, Korea Institute of Science and Technology (KIST), Seoul, Korea (Republic)*

Traditionally, different fields have adapted conventional approaches to resolute the issues in such disease control and environmental health. However, as we come to realize, the ineffectiveness of the conventional approaches has render us to seek out new approach with novel tool and that is nanotechnology. In order to meet the needs, we have developed various nanotechnology-based platforms using multidisciplinary approach. Using the concepts of material science, chemistry, physics, biology and biomedical engineering has enabled us to develop the approach to address critical questions of our primary field of interest. The field of interest is in disease control such as detecting earlier stage of cancer (prostate cancer, colon cancer, and pancreatic cancer) and trace amount of contagious pathogens (pathogenic virus and bacteria) via nanotechnological approach. Here, I will introduce our state of the art nanotechnology-based platforms with a focus of nanodevice-based approach for various clinical applications.

Near-Field Electrospinning of Polyethylene oxide Nanofiber for C2C12 Myoblast Cell Growth Orientation Control
Technical Presentation. NEMB2018-6146

***ILHO SEO, Ji Hong Min, Sungyeun Yang, Won-Gun Koh, WONHYOUNG RYU**, Yonsei University, Seoul, Korea (Republic)*

Electrospinning is a popular nano-engineering technique for nanoscale fiber deposition. It can rapidly fabricate nanofibers with a simple setup in an ambient condition unlike other nanofabrication methods. For these advantages, electrospinning has been applied to diverse applications such as biosensors, medical devices, and tissue scaffolds. Despite this versatile potential, electrospinning is not generally considered as a pattern printing method due to its intrinsic instability, called whipping phenomenon. To overcome this instability, near-field electrospinning (NFE) was suggested for nanoscale pattern printing technique, in which a distance between a printing nozzle and a collector substrate is reduced to collect a fiber within the stable zone of electrospinning. For tissue engineering, highly aligned cell orientation is essential for cell proliferation and differentiation. Although there are many nanoscale pattern printing procedures for cell alignment, most of methods requires expensive equipment and limited materials for the printing.
On the other hand, NFE is a low-cost fabrication technique and can use various biocompatible materials as its printing inks. Herein, we fabricated highly aligned nanofiber molds using NFE in order to control the growth orientation of C2C12 mouse myoblast cell. Polyethylene oxide (PEO) was dissolved in deionized water as a printing ink solution with 5 wt% concentration.
A custom built NFE system, which composed of a high voltage supplier, a high-speed precision x-y micro stage, a nozzle, and a syringe pump for continuous ink supply, was used to fabricate nanoscale fiber molds on a silicon wafer substrate. In order to fabricate a mold with optimum fiber dimension, a parametric study was performed by varying operation parameters such as applied voltage, solution feed rate, working distance between a nozzle and a silicon substrate. PEO nanofibers with average diameter 0.7 um and the spacing of 20 um were deposited on a silicon substrate of 20 mm x 10 mm size. Afterwards, the PEO nanofiber deposited silicon wafer was replicated to a polystyrene (PS) mold. The C2C12 myoblasts were cultured on the PS mold after 3 days and dyed with FITC and DAPI for fluorescence microscopy. Using ImageJ, the cell orientation angle was measured. The C2C12 cells were randomly dispersed on the non-patterned mold group. On the other hand, the C2C12 cells (almost 40 % of cells) were highly aligned on the nanofiber deposited mold group. The cytoskeletal fibers also attached along the nanofiber pattern on the mold.

Positioning and induced collapse of microbubbles
Technical Presentation. NEMB2018-6173

***Nicole Hashemi**, Iowa State University, Ames, IA, United States*

We report spatial control and induced collapse of targeted microbubbles (MBs). Cavitation is known to be present in many situations throughout nature. Controlled cavitation methods could help better understand traumatic brain injuries (TBIs) and explain how neurons respond at moments of trauma. Our approaches involve an ultrasonic transducer and biocompatible Polycaprolactone (PCL) microfibers. These methods provide more control and efficiency compared to previous techniques found in literature. We specifically model three-dimensional spatial control of individual MBs using a 1.6?MHz transducer. Using a 100?kHz transducer, we also illustrate induced cavitation on an individual MB that is adhered to the surface of a PCL microfiber.

Active Antioxidizing Polymer Particle for On-Demand Pressure-Driven Molecular Release
Technical Presentation. NEMB2018-6194

***Yongbeom Seo**, University of Illinois at Urbana-Champaign, Urbana, IL, United States, **Hyunjoon Kong**, University of Illinois At Urbana-Champaign, Champaign, IL, United States*

Overproduced reactive oxygen species (ROS) are closely related to various health problems including inflammation, infection, and cancer. The abnormally high ROS level can cause serious oxidative damage to biomolecules, cells, and, tissues. A series of nano- or micro-sized particles has been developed to reduce the oxidative stress level by delivering antioxidant drugs.

However, most systems are often plagued by the slow molecular discharge driven by diffusion. In this work, we demonstrate an active antioxidizing polymeric particles that can increase the internal pressure in response to the abnormal ROS level and thus actively discharge antioxidants to protect cells and tissues from the oxidative damage. The on-demand pressurized particles particle was assembled by simultaneously loading water-dispersible manganese oxide (MnO2) nanosheets and green tea-derived antioxidant into poly(lactic-co-glycolic acid) (PLGA) spherical shell. In the presence of H2O2, one of the ROS, MnO2 nanosheets in the PLGA particle generated oxygen gas by decomposing H2O2 and increased the internal pressure. Accordingly, the active antioxidizing particle system could release a larger fraction of antioxidants and effectively protect endothelial cells and brain tissues from H2O2-induced oxidative damage. We believe that this study would significantly impact current design paradigm of the controlled molecular releasing system and subsequently improve the efficacy of a broad array of molecular cargos.

TRACK 7
Plenary Speakers

7-5
PLENARY SESSION V
Los Angeles, OMNI Hotel, Bunker Hill Room
2:00pm - 2:50pm

Session Organizer: **Gang Bao**, *Rice University, Houston, TX, United States*

Implementation of Liquid Biopsy Technologies for Clinical Use in Cancer

Plenary. NEMB2018-6284

Stefanie S. Jeffrey, *Stanford University, Stanford, CA, United States*

Patient demise from cancer is generally due to metastatic spread and growth in organs away from a cancer?s site of origin. Cancer cells or other tumor-related products in bodily fluids, such as blood, urine, and saliva, are being investigated to aid in understanding the biology of cancer progression and to help guide cancer care within multiple contexts. Numerous ingenious devices have been developed for capturing and/or analyzing one or more components of liquid biopsy. However, prior to clinical use, liquid biopsy platforms must undergo rigorous testing to demonstrate analytical validity, clinical validity, and, most important, clinical utility. This lecture will discuss various components of liquid biopsy, examples of technologies, and hurdles that must be overcome prior to use of a specific technology platform in the clinic.

TRACK 2
Nano/micro fluidics

Track Organizer: **Cagri Savran**, *Purdue University, West Lafayette, IN, United States*
Track Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

2-5
NANO/MICRO FLUIDICS WITH NOVEL STRUCTURES AND PROPERTIES
Los Angeles, OMNI Hotel, Museum B
3:00pm - 4:20pm

Session Organizer: **Jonghoon Choi**, *Chung-Ang University, Seoul, Korea (Republic)*
Session Co-Organizer: **Weian Zhao**, *University of California, Irvine, Irvine, CA, United States*

Volume of Fluid Modeling of Liquid Water Dynamics in Mixed-Wettability Carbon Papers

Technical Presentation. NEMB2018-6114

Zhiqiang Niu, *UCI, Irvine, CA, United States*, ***Yun Wang***, *UC Irvine, Irvine, CA, United States*, ***Kui Jiao***, *Tianjin University, Tianjin, Tianjin, China*

This study proposes a three-dimensional (3D) volume of fluid (VOF) model to investigate liquid water dynamics in the gas diffusion layer (GDL) of PEM fuel cells and the impact of porosity and wettability on liquid water distribution. A stochastic method is adopted to reconstruct the three-dimensional (3D) microstructure of Toray carbon paper with constant and experimentally-determined spatially varying porosity (TGP-H-060), respectively. The VOF predictions for untreated GDL and the polytetrafluoroethylene (PTFE) treated (PTFE 20 wt%), respectively, are compared with the experimental data of local water distribution that were obtained by the X-ray tomographic microscopy (XTM). The dynamics of water profile and air-water interface are presented to show local liquid water accumulation and breakthrough in GDLs. We find that the spatially varying porosity may have a considerable impact on liquid water distribution in GDLs and a large pressure difference is necessary for liquid water breaking through hydrophobic GDLs.

High Surface Area 3D Microfluidic Reactors with DOE Optimized Photocatalytic Titania for Efficient Water Treatment

Technical Presentation. NEMB2018-6128

Duncan Ashby, Pranee Pairs, Yibo Jiang, Kairui Xia, Vinh Nguyen, Kenneth Ply, Bryan W.K. Woo, Taylor Beaulieu, *University of California, Riverside, Riverside, CA, United States*, ***Phillip Christopher***, *University of California, Santa Barbara, Santa Barbara, CA, United States*, ***Masa Rao***, *University of California, Riverside, Riverside, CA, United States*

Astronaut crews aboard the International Space Station (ISS) rely on recycled water from cabin condensation and urine to sustain their daily water intake. An essential component of the Water Recovery System (WRS) is a thermal catalytic oxidation reactor operating at high pressure and temperature to eliminate volatile organic compounds. Deep space travel and long-term life support systems represent resource sensitive environments that could benefit from alternative reliable, low-cost, and low-energy microfluidic devices to achieve ambitious new goals. Interest in photocatalytic TiO2 microfluidic reactors for applications in water treatment has grown considerably over the past decade. Advantages of microfluidic devices over traditional packed-bed thermal oxidation systems include: operation at standard temperature and pressure, increased surface area to volume ratio, and greatly reduced mass diffusion length, which can translate to enhanced performance on a miniature scale. However, low volumetric throughput remains a critical limitation in many applications, as does the difficulty associated with integrating TiO2 uniformly within complex microfluidic device geometries.

Herein, we present our recent efforts to optimize growth of nanoporous TiO2 (NPT) for use within Ti-based microfluidic devices using a Taguchi multi-criteria study. NPT is grown in situ, directly from the Ti channel surfaces, using a H2O2-based oxidation process. Advantages of this approach include: a) conformal catalyst coverage of complex geometries; b) high porosity yielding increased surface area and fluidic accessibility; and c) potential for scalable fabrication of large area photocatalytic devices with increased volumetric throughput. Additionally, we propose that introducing a novel high-density, high-aspect-ratio micropillar array within the reaction chamber to serve as a scaffold for NPT oxidation will yield significant performance enhancements to overcome the majority of microreactor limitations.

Using Taguchi design of experiments and grey relational analysis the optimal NPT growth conditions were determined through examination of methylene blue degradation and SEM image contrast analysis. Our studies identified the key oxidation parameters responsible for photocatalytic performance. The parameter study led to a film that strikes a balance between maximizing reaction rate and minimizing crack size to produce an efficient, high-quality catalyst. These ideal growth conditions were applied to a Ti deep reactive ion etched (DRIE) micropillar array to form NPT in situ and demonstrated a notable improvement in photocatalytic response compared flat NPT films. Collectively, these results represent important steps towards our goal of developing robust, high-performance multi-scale photocatalytic microreactors with complex channel geometries for increased mass and photon transfer efficiency.

Numerical Study of Mixing Enhancement in a Patterned Micro Channel with Trapezoidal Obstacles

Technical Presentation. NEMB2018-6154

Abhishek Banerjee, Ameeya kumar Nayak, *Indian Institute of Technology Roorkee, Roorkee, India*

Achieving enhanced mixing between various flow streams in
Micro/nano fluidic systems is a great challenge in the prospective of

Biological and chemical processes such as Lab-On-a Chip (LOC), drug delivery in a controlled system, micro-electrical mechanical systems (MEMS) etc. This paper presents a numerical overview of the mixing enhancement using a staggered grid based finite volume approach on Poisson-Nernst-Planck transportation model due to a geometric and surface modulated microfluidic system. A suitable coordinate transformation is used to synchronize the asymmetrically arranged trapezoidal edged surfaces. The mixing improvement is compared and stated for the asymmetric zeta potential with the variation of external electric field. The flow velocity impacts a large influence on mixing (with convective/ diffusive effects) which is justified through the ionic concentration.

Adsorption Behavior of Bone Morphogenic Protein (BMP-2) on Nanoscale Topographies

Technical Presentation. NEMB2018-6265

Izabele Marquetti, *North Carolina A&T State University, Greensboro, NC, United States*, ***Salil Desai***, *North Carolina A&t State Univ, Greensboro, NC, United States*

Nanoscale topographies mediated with biomolecules play a vital role in cellular differentiation and proliferation. Bone morphogenetic proteins (BMPs) are an important class of growth factors directly involved in many developmental processes for tissue and organ restoration. BMP-2 is primary growth factor that directs osteogenic (bone) tissue formation in stem-cell based tissue regeneration. Although different experimental approaches have been explored, the investigation of the molecular models for protein-substrate interaction is warranted for the control of cellular functions. In this research, molecular dynamics (MD) simulations were implemented to study the adsorption behavior of bone morphogenetic protein-2 (BMP-2) on topographically pattern substrates. BMP-2 growth factor was encapsulated in a saline media (0.15 mol/L NaCl) to mimic physiological conditions. MD simulations were performed using Nanoscale Molecular Dynamics (NAMD) source code with the CHARMM27 force field and parallel computing on graphical processing units (K-40 NVIDIA® GPUs). Simulations were executed at 310K for 20ns with periodic boundary conditions. Adsorption of BMP-2 on the substrate was measured by the non-bonded energy, which includes Van der Waals and electrostatic energies of the protein-substrate interaction.

Hydrophobic gold (Au) and hydrophilic silicon nitride (Si3N4) substrates were patterned with both linear gratings (pitch 10nm) and square pillars (5nm x 5nm), respectively. The influence of aspect ratio and feature spacing on the adsorption behavior of BMP-2 was investigated. RMSD and potential energy values indicated rapid unfolding of protein for Si3N4 substrates with linear gratings. This was confirmed by large variations in the radius of gyration and increase in adsorption energies. Orthogonal protein orientations which include side-on and end-on configurations displayed distinctive adsorption behaviors. Protein unfolding was observed for most orientations with preferential binding of residues within the vicinity of the substrate. Nanostructured square pillars in gold presented a super hydrophobic interaction (contact angle ~ 150°) with the protein preserving most of its secondary structure with minor reduction of the ?-sheet structures. For the gold substrate, the presence of salt ions interfered with the protein adsorption forming a barrier layer between the protein and the substrate resulting in weaker interaction. Whereas, linear grating nano patterns on Si3N4 resulted in stretching of the protein leading to its denaturation. The structural stability of the protein was destroyed by the unwinding of the ?-sheet and ?-helix into non-conformal coiled structures. This research presents new insights into the effect of topographical patterning on the adsorption behavior of BMP-2 on biomaterials with contrasting wetting behaviors.

Preparation of microfluidic channels for the habitat and the controlled eradication of bateria and biofilm

Technical Presentation. NEMB2018-6214

Jonghoon Choi, *Chung-Ang University, Seoul, Korea (Republic)*

In recent years, there have been a lot of problems associated with bacteria, especially super bacteria, which have a strong resistance against antibiotics. In this work, we prepared microfluidic channels to grow and assess the biofilm on their surface. Successfully grown biofilm inside microfludic channels was employed as a platform for evaluating novel antibacterial nanomaterials. Graphene oxide (GO) nanosheets, a two-dimensional carbon material, displayed inhibition effects of bacterial growth on its surface. The inhibition effect was demonstrated on GO nanosheets with both Gram-positive and Gram-negative bacteria. In addition, metal nanoparticles such as copper and silver have also well known as antibacterial agents for centuries. Herein, we successfully synthesized silver and copper nanoparticles supported onto GO surface (Ag/Cu/GO) by an effective chemical reduction method and demonstrated the antimicrobial effects against several species of bacteria.

TRACK 5
Nano biosensors for molecular analysis

Track Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*

Track Co-Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

5-4
IMAGING-BASED CELL AND TISSUE BIOSENSORS
Los Angeles, OMNI Hotel, Hershey Room 3:00pm - 4:20pm

Session Organizer: **Alexander Revzin**, *Mayo Clinic, Rochester, MN, United States*

Label-Free Fluorescence Lifetime Techniques for Intraoperative Real-Time Detection of Surgical Margins

Keynote. NEMB2018-6279

Laura Marcu, *University of California, Davis, CA, United States*

Fluorescence lifetime provides a powerful means of achieving label-free molecular contrast for a broad range of biological and medical applications. This presentation will focus on research for development of practical fluorescence lifetime spectroscopy and imaging systems for in vivo studies of heterogeneous samples such as biological tissues. The basic principles, engineering challenges and solutions will be discussed. Emphasis will be placed on recently developed devices and methods enabling real-time characterization and diagnosis of diseased tissues during clinical interventions. I will present studies conducted in human patients demonstrating the ability of our lifetime techniques to provide rapid in situ assessment of tissue biochemical and metabolic features as well as their potential to guide biopsy and surgical procedures including robotic surgery. Representative applications of our techniques assessment of tumor margins intraoperatively will be presented.

Transforming FLIM into a High-Content Molecular Analysis Platform

Technical Presentation. NEMB2018-6113

Maha Rahim, *UC Irvine, Irvine, CA, United States*, ***Enrico Gratton, Jered B. Haun***, *University of California, Irvine, Irvine, CA, United States*

Tumors are complex and heterogeneous; therefore, diagnostic techniques will have to comprehensively assess molecular features across diverse cell types and functional states. Current methods that can provide both spatially-resolved and quantitative molecular interpretation of tissues are limited in multiplexing capacity or are complex and time-consuming. To address these limitations, we have developed a multiplexed imaging platform that utilizes fluorescence lifetime imaging microscopy (FLIM). Fluorescence lifetime refers to the duration of fluorescence light emission after excitation, and it can be leveraged to resolve fluorescent probes that emit the same color. Moreover, the phasor approach to FLIM greatly simplifies lifetime analysis. Instead of fitting complicated exponential functions, the phasor approach provides a graphical representation that enables the unmixing of more than one lifetime using simple geometrical considerations. In this study, we are developing new methodologies to quantitatively detect 4 fluorescent probes within the same spectral window using FLIM and the powerful phasor method. FLIM and phasor studies were performed using 4 different fluorescent probes, 2 organic dyes and 2 quantum dots, that emitted light within the same emission window, but had unique lifetimes. We performed FLIM and phasor analysis on probes in solution to confirm their distinct phasor locations. Next, we conjugated these probes to monoclonal antibodies targeting relevant cancer biomarkers. The phasor locations for each antibody conjugate targeted onto cells closely matched the solution measurements. Simultaneous targeting of spatially-separated biomarkers Ki67 (nucleus), cytokeratin (cytoplasm), and EpCAM (surface) resulted in a distinct phasor map corresponding to various lifetime mixtures of all three probes. Moreover, points on the phasor plot were traced back to pixels within the image, enabling clear visualization of all targets within the cell.

Next, we targeted the cell surface markers EpCAM, Her2, E-Cadherin, and Transferrin Receptor on a panel of cell lines with varying biomarker expression levels, which resulted in distinct phasor mapss. After unmixing the probe signals, intensities for each correlated well with biomarker expression levels measured by flow cytometry. To our knowledge, this is the first demonstration in which 4 probes were resolved based only on fluorescence lifetime.

To fully maximize the potential of this technology, we will extend this detection platform to other spectral windows, resulting in detection capacity on the order of 16-24 targets. The extensive level of molecular information offered by our technology would make it possible to richly characterize heterogeneous tumor specimens to improve detection and enable host-cell subtyping, and rare cell detection.

Thermally-drawn Microprobe Impedance Sensor for Vulnerable Plaque Detection

Technical Presentation. NEMB2018-6144

DaSom Yang, JIYONG LEE, WONHYOUNG RYU*, Yonsei University, Seoul, Korea (Republic)*

Vulnerable plaque is formed by the accumulation of cholesterol in the blood vessel walls. When plaque grows gradually in the artery, it narrows the blood vessel and reduces the blood flow. Although vulnerable plaque itself does not have any noticeable sign or symptom, its unstable state prone to sudden rupture which could lead the myocardial or cerebral infarct. Thus, early diagnosis of vulnerable plaque is highly desired. Currently, CT angiography or intravascular ultrasound is used to diagnose the vulnerable plaque in clinics. These imaging-based diagnostic are measuring the anatomical obstruction or hyperplasia of arteries. However, those anatomic images are insufficient for distinguishing stable plaque from vulnerable plaque. The main difference between stable and vulnerable plaque is not their anatomical structures but their compositions; stable plaque has strong thick fibrous caps while vulnerable plaque is composed of a large lipid-rich core and thin fibrous caps which is easy to rupture. Thus, it is highly desired to have a method to locally analyze the tissue components for improving the diagnostic accuracy. Electrical impedance spectroscopy(EIS) can measure the electrical characteristics of living tissue according to the frequency. Since the measured impedance varies depending on the tissue type and components, EIS can identify the plaque composition and possibly diagnosis whether they are stable or vulnerable. Recently, planar microelectrodes were reported to diagnose vulnerable plaque by measuring EIS. However, to make a stable contact at the curved surface of inner blood vessel wall, those planar structures require a high pressure which could lead the plaque rupture. In addition, since it blocks the blood flow during the measurements, any delay of measurement can risk patient?s health seriously. In this study, we developed a microprobe-type flexible electrodes to measure the local electrical property of tissues. Since high aspect ratio microprobe structures enable precise positioning and fine contact at blood vessel wall without neither block nor pressure the blood vessel, they could reduce the risk of rupture. Conducting composite polymer(MWCNT/SU-8) microprobes were fabricated on a flexible screen-printed electrode by thermal drawing. Electrochemical properties of fabricated microprobe sensors were evaluated by cyclic voltammetry (CV). CV results confirmed that the composite microprobes functioned as electrodes properly for electrochemical analysis. EIS was conducted with two types of biological tissues: lean and fat. EIS results showed that the microprobe type electrodes could distinguish the vulnerable plaque much better than a planar type electrode because of their high current density.

Engineering DNA Origami Structures On Cell Surface for Detection of Cancer Biomarkers in Cellular Microenvironment

Technical Presentation. NEMB2018-6169

Melika Shahhosseini, Ehsan Akbari*, Ohio State Universoty, columbus, OH, United States*, ***Jonathan W. Song****, Ohio State University, Columbus, OH, United States*, ***Carlos E. Castro****, Ohio State Universoty, columbus, OH, United States*

Cancer cells exhibit specific gene mutations, such as mutations in the tumor suppressor gene BRCA1 that are observed in breast cancer [1]. Circulating tumor DNA (ctDNA) are the mutated genes that are released by dead cancer cells into blood circulation, which presents a potential marker for early stage diagnosis. There are currently multiple methods to detect ctDNAs for early cancer diagnosis, normally by performing liquid biopsies. However, current detection methods have limitations such as demand for specialized equipment, low sensitivity and insufficient specificity [2]. Furthermore, none of the available techniques provide in-situ detection, which may provide the additional benefit of elucidating mechanisms of cancer progression mediated by ctDNA. To address these limitations, we aim to exploit cells as sensing platforms by engineering their cell membranes to detect ctDNA in-situ with fluorescence based reporting.

DNA origami is self-assembly of geometric complex nanostructures using DNA as building blocks. We recently reported a highly novel approach to engineer cell-membrane function by embedding DNA-origami nanodevices onto the cell surface via cholesterol-conjugated oligonucleotides as amphiphilic anchors [3]. We programmed DNA origami nanodevices to detect presence of 2 different DNA sequence (targets) on the cell surface by emitting fluorescence signal in two different channels.

Preliminary results show that introduction of each DNA target at 1μM, increases fluorescence signal by 50%. Also, structures are able to simultaneously detect two target DNA sequences over a broad range of concentrations (1nM to 1μM). Preliminary results also suggest we can detect binding events on individual cells, and in some cases with sub-cellular resolution. Therefore, we expect that implementing DNA origami structures on cell membranes will enable us to profile the spatiotemporal distribution of ctDNA in cellular microenvironment.

For future steps, we plan to incorporate multiple cancer-related aptamers into DNA structures to enable simultaneous detection of multiple cancer biomarkers. Specifically, we are interested in detection of combinations of different cancer-related genes with other cancer biomarkers (e.g. platelet-derived growth factor and pH) in cellular microenvironment. This technique can be implemented as a highly sensitive liquid biopsy method for early detection of cancer.

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TRACK 6
Nanophotonics for biomedical imaging

Track Organizer: **yadong yin**, *University of california riverside, Riverside, CA, United States*
Track Co-Organizer: **peter yingxiao wang**, *UC San Diego, La Jolla, CA, United States*

6-4
ADVANCED IMAGING PROBES
Los Angeles, OMNI Hotel, Museum A 3:00pm - 4:20pm

Session Organizer: **Eric Ahrens**, *UC San Diego, La Jolla, Mayotte*
Session Co-Organizer: **Xiaoping Hu**, *University of California-Riverside, Riverside, CA, United States*

Towards the Development of MRI Reporter Gene

Keynote. NEMB2018-6253

Xiaoping Hu*, University of California-Riverside, Riverside, CA, United States*

In molecular imaging with MRI, targeted MRI contrast agents are used to map cellular or molecular activities in vivo. Magnetic iron oxide nanoparticles, owing to their high relaxivity, are often the agent of choice, particularly for labeling cells to be tracked with MRI. However, there are limitations with iron oxide nanoparticle labeling as the labels are passive and can be diluted with cell division and the externally labeled particles cannot be used to actively monitor biomolecular activities such as gene expression. In optical imaging, reporter genes, such as green fluorescent protein and luciferase, have been widely used to monitor molecular activities in cells, tissue and animals. Yet, optical imaging cannot be used to image large animals or humans due to limitations in optical penetration.
Therefore, there is a great need for MRI reporter genes for in vivo imaging. To this end, we exploited genes from magnetotactic bacteria, which produces iron-oxide nanoparticles of 50-200 nm in diameter. The first gene we tested is magA, which codes for a protein that acts as an iron transporter. When expressed in 293ft cells, an immortalized human kidney cell line, produced nanoparticles that are 5-10 nm in diameter. More importantly, the mammalian cells expressing magA also exhibited a significant MRI contrast, making them visible in MRI images. The other bacterial gene that we worked with was mms6, which codes for a protein that is a key player in the magnetic nanoparticle formation in the bacteria. The expression of mms6 in 293ft cells also generated clearly visible MRI contrast. In addition, the expression of mms6 in cells exogenously labeled with magnetic iron oxide nanoparticles also increased the retention of nanoparticles in cells undergoing division. In summary, we have demonstrated the potential of magA and mms6 for MRI reporter genes and the utility of mms6 for extending the retention of magnetic nanoparticles labels.

Long-term imaging of cerebral blood flow through an ageing-resistant transparent nanocrystalline yttria-stabilized-zirconia cranial implant
Student Competition Presentation. NEMB2018-6180

Nami Davoodzadeh, *University of California, Riverside, Riverside, CA, United States*, ***Mildred S. Cano-Velazquez***, *Universidad Nacional Autonoma de Mexico, Mexico City, Select State/Province, Mexico*, ***David Halaney, Carrie R. Jonak, Devin Binder, Guillermo Aguilar***, *University of California, Riverside, Riverside, CA, United States*

Laser-based diagnostics and therapeutics show promise for many neurological disorders. However, the poor transparency of cranial bone limits the spatial resolution and interaction depth that can be achieved. This problem has previously been addressed in animal studies by removing or thinning the skull to transparency. However, a permanent and reliable solution has not yet been developed. Our study demonstrates a new method to address this challenge in biomedical imaging research, through the use of novel transparent cranial implants made from nanocrystalline yttria-stabilized zirconia (nc-YSZ) to provide chronic optical access to the brain. Although zirconia-based implants have been known for their excellent mechanical properties, the in vivo application was found to be affected by long-term failures. Accelerated aging simulations over long periods typically transforms the ceramic structure. In this study we show the nanostructured implants can withstand extended ageing treatments which simulate conditions equivalent to several decades of ageing in vivo. To compare the higher transparency of the ageing-resistant cranial implants relative to native cranial, we performed Laser Speckle Imaging (LSI) of underlying brain in an acute murine model. LSI have attracted extensive attention recently because they can image cerebral blood flow with high spatiotemporal resolution. Our results provide further evidence supporting the feasibility of an nc-YSZ transparent cranial implant as a clinically-viable long-term optical access on a chronically-recurring basis, thereby suppressing the need for repeated craniotomies. Successful development of the use of this implant joined with this imaging method has the potential to advance the study of neuropathologies or novel neuro-procedures in animal models where measurement of cerebral blood flow is of interest, such as blood flow changes during stroke, changes in blood flow due to functional activation, and spreading depolarization and its role in brain injuries, pathophysiology of migraine, and subarachnoid hemorrhage.

Designing novel imaging probes and methods for clinical fluorine-19 MRI cell tracking
Keynote. NEMB2018-6262

Eric Ahrens, *UC San Diego, La Jolla, Mayotte*

Development of cell therapies, such as stem cell and immunotherapies, could be accelerated by adopting non-invasive imaging modalities to visualize the behavior and movement of cells following transplantation. Our interdisciplinary laboratory focuses on adapting MRI to visualize specific cell populations in the body. An approach that we are developing is called ?in vivo cytometry? that offers background-free hot-spot imaging of cells and quantitative capabilities. Cell populations of interest are detected in vivo with high specificity using 19F MRI perfluorocarbon (PFC) nanoemulsion imaging probes designed for cell labeling that do not affect cell function. Clinical translation of in vivo cytometry has recently been demonstrated in a pilot trial treating colorectal cancer using immunotherapeutic dendritic cells. The current status of additional in vivo cytometry trials to treat glioma and head-neck cancers will be described. PFC nanoemulsions can also be formulated to label macrophages in situ to visualize sites of inflammation in vivo. Preclinical inflammation image data in the areas of neuroinflammation, autoimmune diseases, organ transplant rejection and cancer will be presented. Dr. Ahrens is a Professor in the Department of Radiology at the University of California, San Diego, and is Director of Stem Cell Molecular Imaging at the Sanford Consortium for Regenerative Medicine, La Jolla, CA.

TRACK 8
Tutorials

8-1
WORKSHOP: NSF FUNDING OPPORTUNITIES
Los Angeles, OMNI Hotel, Museum A 4:30pm - 5:20pm

Session Organizer: **Chenzhong Li**, *National Science Foundation, Alexandria, VA, United States*
Session Co-Organizer: **Bumsoo Han**, *Purdue University, West Lafayette, IN, United States.*

TRACK 7
Plenary Speakers

7-6
PLENARY SESSION VI
Los Angeles, OMNI Hotel, Bunker Hill Room 8:00am - 8:50am

Session Organizer: **Song Li**, *University of California, Los Angeles, Los Angeles, CA, United States*

Deep Learning-enabled Computational Imaging and Sensing
Plenary. NEMB2018-6290

Aydogan Ozcan, *Electrical and Computer Engineering Department, Los Angeles, CA, United States*

Deep learning is a class of machine learning techniques that uses multi-layered artificial neural networks for automated analysis of signals or data. The name comes from the general structure of deep neural networks, which consist of several layers of artificial neurons, each performing a nonlinear operation, stacked over each other. Beyond its main stream applications such as the recognition and labeling of specific features in images, deep learning holds numerous opportunities for revolutionizing image formation, reconstruction and sensing fields. In this presentation, I will provide an overview of some of our recent work on the use of deep neural networks in advancing computational microscopy and sensing systems, also covering their biomedical applications.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-7
MODULATION OF NANOPARTICLE DELIVERY
Los Angeles, OMNI Hotel, Museum A 9:00am - 10:20am

Session Organizer: **Daniel J. Hayes**, *The Pennsylvania State University, UNIVERSITY PARK, PA, United States*

Immune microenvironment of tumors determines uptake and retention of nanoparticles.
Keynote. NEMB2018-6264

Robert Ivkov, Preethi Korangath, James Barnett, *Johns Hopkins University School of Medicine, Baltimore, MD, United States*, ***Anirudh Sharma***, *University of Minnesota, Minneapolis, MN, United States*, ***Elizabeth Henderson, Jackie Stewart***, *Johns Hopkins University School of Medicine, Baltimore, MD, United States*, ***Sri Kamal Kandala***, *Johns Hopkins University, Baltimore, MD, United States*, ***Chun-Ting Yang, Todd Armstrong, Elizabeth Jaffee***, *Johns Hopkins University School of Medicine, Baltimore, MD, United States*, ***Cordula Gruettner***, *micromod Partikeltechnologie, GmbH, Rostock, Germany*, ***Sara Sukumar, Brian Simons***, *Johns Hopkins University School of Medicine, Baltimore, MD, United States*

Nanoparticle-based cancer therapy and drug delivery has advanced significantly in recent years, providing new opportunities. Significant deficiencies in knowledge remain to explain nanoparticle delivery and distribution to (solid) cancer tumors. Results of clinical trials often fail to recapitulate preclinical experience, implying that model-specific features, which do not accurately reflect clinical realities, are unknowingly incorporated into nanoparticle design. It has been recognized for some time that the unique properties of nanoparticles lead to interactions with components of host immune systems; but, less understood is how these interactions affect uptake and distribution in cancer tumors. We sought to systematically study the impact of the host immune system, targeting, and tumor biology on the distribution of ferrite nanoparticles in mouse models of HER2 overexpressing breast cancer by varying the tumor and immune status of the host. We show that tumor-associated immune cells play a major role in the uptake and distribution of antibody conjugated nanoparticles across xenograft models, with implications that host immune status is also a factor. We also developed an allograft model of human HER2 overexpressing breast tumor that spontaneously develops in immunocompetent transgenic mice (FVB/N background). Using this model we compared the uptake and retention of a given nanoparticle construct in different immune stratified mouse models, using the same tumor, ranging from most immunocompromised to fully immune-competent models. Results of these studies will be presented indicating a passive uptake mechanism is unsupported by our results.

Magnetic Heating Properties of Ferromagnetic CoFe Nanowires for Nanowarming Cryopreserved Tissues
Technical Presentation. NEMB2018-6177

Daniel Shore, *University of Minnesota, Minneapolis, MN, United States*, ***Adrian Ghemes***, *Iasi university, Iasi, Romania*, ***Oana Dragos-Pinzaru***, *National Institute of R&D for Technical Physics, Iasi, Romania*, ***Zhe Gao, Ibro Tabakovic***, *University of Minnesota, Minneapolis, MN, United States*, ***John Bischof, Bethanie Stadler***, *Univ Of Minnesota, Minneapolis, MN, United States*

Successful cryopreservation of organs requires controlled cooling and rapid, uniform heating rates over large volumes. This work highlights recent advancements to address these challenges using carefully engineered, high magnetization, high aspect ratio, PEG-coated CoFe nanowires suspended in VS55 cryoprotective agent for nanowarming tissues using an alternating magnetic field (AMF), 20 kA/m and 360 kHz. First, 8 µm CoFe, Fe, Co, and Ni (Ms = 245, 218, 160, and 53 emu/g, respectively) nanowires were made, by electrodeposition in anodic aluminum oxide (AAO) templates, to compare how the saturation magnetization (Ms) affects the specific absorption rate (SAR) for the nanowires. Magnetic hysteresis loops were measured with the nanowires aligned, in AAO, parallel and perpendicular to the applied field. The highest Ms CoFe nanowires had the largest area inside the hysteresis loop, and they had the highest SAR values (in glycerol), followed by Fe, Co, and Ni. These results agree with the theoretical equations for maximum heating rates. Next, the CoFe nanowire lengths (1-16 µm) and concentrations (0.5-10 mg/ml) were adjusted to study how they affect the SAR in glycerol. The SAR increased with increasing nanowire length, with higher SAR at 0.5-1 mg Fe/ml. In addition, a solenoid was used to align the nanowires parallel with the AMF, prior to heating, and this alignment increased the SAR by more than 200%, compared with randomly oriented nanowires, up to SAR = 2960 W/g Fe for 8 µm CoFe nanowires, 1 mg/ml. Aligning the nanowires parallel with the AMF decreases the AMF magnitude needed to flip the magnetizations of the nanowires. More magnetic domains in the nanowires will flip using lower AMFs, therefore more heat energy is generated by this magnetic work. These encouraging results in glycerol were translated into nanowarming of nanowires in cryogenically vitrified VS55, starting from -185°C. The heating rates for the CoFe NWs, 150-567°C/min (1-5 mg/ml) were well above the critical warming rate for VS55 (55°C/min), and much faster than rates for commercial iron oxide nanoparticles, using fraction of the typical concentration, 10 mg/ml. Increasing the AMF to 25 or 30 kA/m dramatically increased the heating rates. The PEG-coated CoFe nanowires in VS55 did not decrease the cell viability of human dermal fibroblast cell at 1 or 2.5 mg Fe/ml. Finally, the CoFe nanowires were used for nanowarming a vitrified porcine artery, to demonstrate the feasibility of the application.

NextGen Sequencing of Adipose Derived Stem Cells for Therapeutic Applications
Technical Presentation. NEMB2018-6199

Shahensha Shaik, *Louisiana State University, Baton Rouge, LA, United States*, ***Elizabeth Martin***, *LSU, Baton Rouge, LA, United States*, ***Daniel Hayes***, *Penn State, University Park, PA, United States*, ***Ram Devireddy***, *Louisiana State Univ, Baton Rouge, LA, United States*

Adipose-derived stem cells (ASCs) are multipotent in nature that can be differentiated into various cells lineages such as adipogenic, osteogenic, and chondrogenic. The commitment of a cell to differentiate into a particular lineage is regulated by the inter-play between various intracellular pathways and their resultant secretome. Similarly, the interactions of cells with the extracellular matrix (ECM) and the ECM bound growth factors instigate several signal transducing events that ultimately determine ASC differentiatiation. In this study, RNA-sequencing (RNA-seq) was performed using an ion torrent sequencer system to identify the transcriptome profile of osteogenically induced ASCs to understand the associated genotype changes. The expression of genes related to osteo-, adipo-, chondro- and angiogenesis was investigated along with the matrisome related, ECM remodeling enzymes such as matrix metalloproteases, integrins, a disintegrin and metalloproteinase with thrombospondin motifs were analyzed. Furthermore, a comparative analysis between the genes encoding secretome in mesenchymal stem cells during osteogenesis with ASCs was also performed. Gene ontology functional annotations analysis using David bioinformatics resources demonstrated the enrichment of pathways associated with ECM organization and angiogenesis. Observed alterations in ECM associated genes included those identified as glycoproteins, collagens, and proteoglycans. In additition mediators of ECM production were also altered between osteogenic and undifferentiated ASCs. The pro-angiogenic markers especially Angpt1, leptin, HGF, were found to be increased in the osteogenic induced ASCs. The RNA-seq data was validated by performing qPCR on selected ECM genes. This analysis suggests that ECM production and adipogenesis in ASCs following osteogenic stimulation is unique compared to undifferentiated ASCs.

A Multiscale Drug Delivery System for 3D Printed Spatiotemporal Control of Stem Cell Differentiation in a 3D Printed Architecture
Technical Presentation. NEMB2018-6175

Guru Venkatesan, Michael McAlpine, *University of Minnesota, Minneapolis, MN, United States*

Functional living tissues and organs fabricated from human induced pluripotent stem cells (iPSCs) have tremendous potential in regenerative medicine and drug development. With a long-term goal to fabricate patient-specific biological implants, teams of multidisciplinary researchers are aiming to develop ways to reliably 3D-print biological materials such as iPSCs, scaffolds and growth factors (collectively referred to as bio-inks) in specific shapes and forms to achieve thick, vascularized, living tissues and organs with native functionalities. One of the primary challenges in this regard is to differentiate printed iPSCs into two or more cell types (for instance, endothelial cells and cardiomyocytes), that are spatially resolved within the same structure. In addition, early or delayed delivery of differentiation factors during the culture process would result in an entirely different cell type or cell death. Therefore, delivery of distinct differentiation factors controlled both in space and time is required.

In order to perform such spatially and temporally controlled delivery of differentiation factors, we are using biocompatible-microcapsules that can efficiently contain and release these molecules upon demand. Pre-fabricated, differentiation factor-carrying microcapsules will then be strategically placed along with the cells and scaffolds during printing. Plasmonic gold-nanorods incorporated in the polymer-layer enable rupture of the shell on demand using a laser, in order to release the differentiation factors.1 These microcapsules are fabricated using a combination of water-oil-water (W-O-W) double emulsion and solvent-casting, wherein the innermost aqueous phase carries both water-soluble and liposoluble differentiators, while the middle phase contains biocompatible polymers and nanorods mixed in organic phase. As the middle organic solvent gradually evaporates, polymer-shelled microcapsules with aqueous cores are formed.

While water-soluble differentiators can be directly dissolved in the aqueous core, liposoluble differentiators (such as IWP2 that is required to achieve cardiomyocytes)2 passively leaks out of the organic phase of the microcapsule, making it inapplicable for the latter. We therefore use liposomes ? a water-soluble, submicron scale drug carrier that can carry small liposoluble molecules incorporated in its hydrophobic regions.3 With such microscale polymer-capsules containing submicron scale liposomal drug carriers, controlled delivery of both water-soluble and liposoluble differentiator molecules can be achieved. Our ongoing research on generation and characterization of these multiscale drug carriers to induce spatiotemporally controlled differentiation of 3D-printed stem cell assembly will be presented.

References

1 Gupta, M. K. et al. 3D printed programmable release capsules. Nano letters 15, 5321-5329 (2015).

2 Lian, X. et al. Directed cardiomyocyte differentiation from human pluripotent stem cells by modulating Wnt/?-catenin signaling under fully defined conditions. Nature protocols 8, 162 (2013).

3 Gulati, M., Grover, M., Singh, S. & Singh, M. Lipophilic drug derivatives in liposomes. International Journal of Pharmaceutics 165, 129-168 (1998).

TRACK 4
Nanomanufacturing and functionalization of biomaterials

Track Organizer: **Song Li**, *University of California, Los Angeles, Los Angeles, CA, United States*
Track Co-Organizer: **Hyunjoon Kong**, *University of Illinois At Urbana-Champaign, Champaign, IL, United States*

4-3
HIGH-THROUGHPUT NANO DEVICES
Los Angeles, OMNI Hotel, Hershey Room 9:00am - 10:20am

Session Organizer: **Paul Weiss**, *UCLA, Los Angeles, CA, United States*
Session Co-Organizer: **Jong Hyun Choi**, *Purdue University, West Lafayette, IN, United States*

Nanotechnology Approaches to Biological Heterogeneity and Cellular Therapies
Keynote. NEMB2018-6239

Paul Weiss, *UCLA, Los Angeles, CA, United States*

The great promise of single-molecule/assembly measurements is to understand how critical variations in structure, conformation, and environment relate to and control function. New approaches to sensing, imaging, and analysis are keys to elucidating these associations. I will discuss current and upcoming advances and will pose the challenges that lie ahead in creating, developing, and applying new tools for biology and medicine. These advances include using biomolecular recognition in sensor arrays to probe dynamic chemistry in the brain and microbiome systems. It also includes fusing spectroscopic imaging modalities and freeing up bandwidth in measurements to record simultaneous data streams and to expand our dynamic range. Recent advances in sparsity and compressive sensing can be applied both to new analysis methods and to directing measurements so as to assemble and to converge structural and functional information. Early examples will be discussed.

Reciprocity of Neurons and Muscle towards Neuromuscular Junction Assembly
Technical Presentation. NEMB2018-6249

EUNKYUNG KO, *University of Illinois at Urbana-Champaign, Urbana, IL, United States*, ***Seung Jung Yu***, *Korea Advanced Institute of Science and Technology, Daejeon, Korea (Republic)*, ***Gelson Pagan-Diaz, Ziad Mahmassani, Marni Boppart***, *University of Illinois at Urbana-Champaign, Urbana, IL, United States*, ***Sung Gap Im***, *Korea Advanced Institute of Science and Technology, Daejeon, Korea (Republic)*, ***Hyunjoon Kong***, *University of Illinois At Urbana-Champaign, Champaign, IL, United States*

Neuromuscular junction (NMJ) is a chemical synapse formed between the motor neurons and skeletal muscle fibers. Usually, it serves a key role in skeletal muscle movement. In this study, we proposed that nano-patterned substrates would enhance better myogenic differentiation of skeletal muscle cells and the resulting patterned muscle fibers would promote neural innervation of the neuronal cells into muscle fibers. To examine the hypothesis we compared the maturity of the myotubes formed on a flat substrate with those on different sizes of linearly patterned substrates and analyzed the neural innervation.
Polyurathane acrylate substrates were prepared by applying PUA resin on the silicon master, covering the top with PET film, then curing the PUA resin with ultraviolet light. The substrates were peeled off from the master, and coated with matrigel prior to seeding cells. Muscle cells were cultured cultured in growth medium for the first 3 days, and exchanged with differentiation medium to induce myotube formation. After a week, neural stem cells were seeded on the muscle layer to induce neuromuscular junction formation. NMJs were immunofluorescently stained to image the presence of acetylcholine receptors, and the functionality was analyzed by treating glutamic acid and curare.

Morphometric study revealed that primary myoblasts cultured on the nano-patterend substrates align to each other better, and exhibit increased actomyosin expression. The patterned substrates provided more focal adhesion points to the cells. Similarly, neural stem cells seeded on the aligned muscle layer expressed more neuronal marker compared to the muscle cells cultured on a flat substrate. The neuronal cells on the patterend myotubes followed the linear morphology of the muscle cells. We confirmed the NMJ formation by immunocluorescently using neurofilament, myosin, and acetylcholine receptor markers. As we analyzed the area of co-localization of 3 markers, expression level was higher on the patterned substrate group.
Our nano-patterend substrates can guide muscle and neural stem cells to form alignment and form NMJ in an orderly manner. The engineered NMJs on the patterned substrates show better functionality since the topography introduces a more in vivo-like environment to the cells.

Programmable Molecular Capture and Release on DNA Origami by DNAzyme-Mediated Logic Gate

Technical Presentation. NEMB2018-6161

Feiran Li, Jong Hyun Choi, *Purdue University, West Lafayette, IN, United States*

Capture and release of functional molecules, proteins, and nanoparticles are important steps toward understanding their properties, harnessing their functionalities, and sorting them based on their species, sizes, or shapes. DNA is perhaps the most promising tool for such purposes, given its programmable self-assembly principle and a wide variety of modifications by chemical groups as well as their responsive to external signals such as light, cations, and pH.

In this work, we introduce a DNA origami-based site-specific molecular capture and release platform operated by a DNAzyme-mediated logic gate process. With the excellent programmability and accessibility of DNA origami, cargos (small molecules, protein and nanoparticles) can be captured onto desired positions on the origami. For cargos in different locations or different types of cargo, a set of DNA inputs can be added as inputs to control the DNAzyme output which is so called DNA logic gate. With an AND gate implemented, both two DNA segments inputs have to be present, otherwise no DNAzyme output will be created. The DNAzyme output could release a target cargo based on its base-pairing. With the incorporation of light sensitive azobenzene moieties in DNA, UV light can break the DNA logic gate process, thus making the cargo unreleased no matter what inputs are added in.

We envision that the DNA platform could be used for analyte studies by realizing precise capture and release. The strategy introduced in this work should also be applicable to other analytes or extended to other external signals with minimal modifications. Besides, it is possible to construct more powerful platforms with appropriate sequence and length designs of DNAzyme such that a minimal amount of DNAzymes and logic gate strands are used for programmable release processes.

Alginate Microfibers for Encapsulating Astrocytes

Technical Presentation. NEMB2018-6174

Nicole Hashemi, *Iowa State University, Ames, IA, United States*

Traditional 2D cell culturing techniques provide a picture of cell conditions, but that picture is incomplete and might be inaccurate. Moving towards 3D cell culturing will provide a more physiologically relevant and highly tunable method for the creation of tissue models for biomedical research and regenerative medicines. Fibrous scaffolds allow for a high degree of control over the physical, mechanical and chemical microenvironment while maintaining excellent diffusion-based transport of nutrients into and waste out of the cell. Mechanical properties such as porosity or elasticity affect these factors, and as such were investigated in this study. In this paper, Rat Astrocyte Cells (RACs) were encapsulated within Alginate microfibers produced using microfluidic spinning. Cells encapsulated in this way were recovered successfully up to 84 hours post encapsulation.

TRACK 6
Nanophotonics for biomedical imaging

Track Organizer: **yadong yin**, *University of california riverside, Riverside, CA, United States*
Track Co-Organizer: **peter yingxiao wang**, *UC San Diego, La Jolla, CA, United States*

6-5
OPTICAL PROPERTIES OF NANOMATERIALS
Los Angeles, OMNI Hotel, Museum B 9:00am - 10:20am

Tumor microenvironment targeted theranostic nanoparticles detected within orthotopic pancreatic tumors using MSOT

Keynote. NEMB2018-6289

Lacey R. McNally, *Departments of Bioengineering and Cancer Biology, Winston-Salem, NC, United States*

Despite significant efforts to translate nanotechnology for cancer application, lack of identification of biodistribution/accumulation of these nanovehicles in vivo remains a substantial barrier for successful implementation of theranostic nanoparticles in the clinic. The purpose of the study was to develop a tumor targeted- theranostic nanovehicle for pancreatic cancer detectable by multispectral optoacoustic tomography (MSOT). To improve the tumor specificity of our mesoporous silica nanoparticle containing wormhole pores (WMSN), we utilized a dual tumor targeting strategy: 1) using an acidic pH responsive targeting ligand, pHLIP, and 2) an acidic tumor microenvironment responsive gatekeeper. The tumor specificity of the W-MSN particle was improved with the addition of both chitosan, targeting acidic pH, and V7 targeting peptide. Drug release assays using the theranostic nanoparticles confirmed pH responsive release of gemcitabine in vitro. The tumor specific uptake of V7-WMSN nanoparticles in the context of extracellular acidic pH was confirmed using propodium iodide within cells. Based upon IR-780 dye encapsulation within the nanoparticles, V7-WMSNs demonstrated increased intensity compared to untargeted WMSNs at both pH 7.4 (7X) and 6.5 (22X); however the signal was much more pronounced at a pH of 6.5 using tissue phantoms ($p<0.05$). In vivo, V7-WMSN particles demonstrated orthotopic pancreatic tumor specific accumulation (65.3 MSOT a.u.) compared to liver (2.1 MSOT a.u.) or kidney (1.2 MSOT a.u.) as identified using multispectral optoacoustic tomography ($p<0.0001$, $p<0.0001$) and confirmed by ex vivo analysis. By tracking in vivo nanoparticle biodistribution with MSOT, it was shown that pH responsive, ligand targeted MSNs preferentially bind to pancreatic tumors for payload delivery.

How Aggregation Changes the Optical Properties and Photothermal Heating of Gold Nanoparticles: A Quantitative Study

Technical Presentation. NEMB2018-6247

Yiru Wang, *University of Minnesota - Twin Cities, Minneapolis, MN, United States*, ***Zhe Gao***, *University of Minnesota, Minneapolis, MN, United States*, ***Zonghu Han***, *University of Minnesota - Twin Cities, Minneapolis, MN, United States*, ***Yilin Liu***, *University of Minnesota, Minneapolis, MN, United States*, ***Huan Yang, Taner Akkin, Chris Hogan***, *University of Minnesota - Twin Cities, Minneapolis, MN, United States*, ***John Bischof***, *Univ Of Minnesota, Minneapolis, MN, United States*

Gold nanoparticles (GNPs) are ideal optical contrast agents, photothermal heat producers, and drug carriers in biomedicine. As quantitative outcomes are increasingly needed at smaller scales, more precise knowledge of GNP performance, especially for heating is required. The geometry, concentration, distribution and interaction with the media create GNP?s bulk heat generation. This heat generation is relatively well understood for idealized conditions but not for complicated real conditions (polydisperse, nonhomogeneously distribution, and/or aggregated systems). While polydispersion and distribution can be controlled in many cases, aggregation often times cannot. For instance, this is often the result when nanoparticles are injected systemically and then accumulate within cells. Additionally, we are unaware of any systematic studies for GNP heating based on aggregation conditions.

Here, we investigate the optical property change of gold nanospheres (5, 16, and 30nm diameter) aggregated to various cluster sizes by numerical and experimental methods. Specifically, aggregation cluster geometries were generated by an algorithm to mimic compact and sparse conditions over a range from 2 to 30 particles per cluster. We then interrogated these clusters computationally using discrete dipole approximation (DDA) to calculate the absorption/scattering/extinction cross section of GNPs of different particle diameters. The simulation results were then compared to experimental photothermal conversion experiments using GNP in a solution within a cuvette irradiated with a 532 nm laser irradiation. [1] Different aggregation conditions (i.e. clusters) were induced by adding NaCl to citrate stabilized GNP solutions and then fixed by transferrin or PVP as suggested by literature. [2] Here we demonstrate ?10% change in optical properties (i.e. value change and peak shift) and photothermal heat generation of the same GNPs depending on aggregation cluster sizes. One interesting result is that the property change is rapid when the cluster is small and then saturates after reaching a critical aggregation cluster size. Another counter-intuitive finding is that very small clusters (2 to 5 GNPs) of 16 nm GNPs can produce more photothermal heat than the same number of particles in mono disperse solution. As the nanoparticle size grows beyond 16 nm, this effect dies away and aggregation leads to less phothermal heat than the same number of particles in solution. Our results could be helpful in designing new multi-particle GNP systems for enhanced heating, or determining precise GNP dose in photothermal applications.

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Coupled Magnetic-plasmonic Anisotropy of Fe3O4@Au Nanorods for Active Multimodality Imaging

Technical Presentation. NEMB2018-6223

Zhiwei Li, yadong yin, *University of california riverside, Riverside, CA, United States*

Engineering multifunctional nanostructures have been intensively used for multimodal biological imaging, but almost invariably with the restriction that contrast agents in conventional platforms passively form separate imaging modal without positive interference. Herein, we propose a reliable approach towards active magnetic resonance/photoacoustic multimodal imaging (MRI/PA), in which the functional components not only serve as contrast agent individually but also couple together for active regulation and synergistic enhancement of imaging contrast. More specifically, uniform Au nanoshells with controllable thickness are coated on Fe3O4 nanorods by local strain-confined seeded growth. The overall size of Fe3O4@Au core/shell nanostructures is about 35 nm in diameter and 120 nm in length with strong longitudinal plasmonic resonance at ~1000 nm. Generally, to minimize magnetic anisotropic energy, the long axis of magnetic nanorods will be parallel to external filed direction. Therefore, in addition to contrast agent in MRI, magnetic nanorods can couple with the plasmonic anisotropy of Au shells, allowing for active modulation of PA signals via external magnetic field. Once the rods are aligned parallel to propagation of NIR excitation light, the longitudinal mode will be suppressed, which in principle deactivates PA modal. Images acquired now exclusively originate from noises and serve as background reference. When they are perpendicular, however, the longitudinal resonance of each nanorod will be fully excited, thus promoting PA signals to the maximum. To further suppress background noises, pixel from reference images will be subtracted for coherent rotation processing. As a result, the active multimodal imaging proposed here rejects any noises from diffuse and localized sources and enhance the contrast specificity of multifunctional nanostructures.

Revealing the Collective Optical Properties of Complex Plasmonic Vesicles

Technical Presentation. NEMB2018-6213

Jaona Randrianalisoa, *University of Reims Champagne-Ardenne, Reims Cedex, France*, ***Xiuying Li***, *University of Texas at Dallas, Richardson, TX, United States*, ***Maud Serre***, *University of Reims Champagne-Ardenne, Reims Cedex, France*, ***Zhenpeng Qin***, *Univ of Texas At Dallas, Richardson, TX, United States*

Vesicular assembly of small plasmonic nanoparticles, or plasmonic vesicle, is a promising multifunctional theranostic platform for photothermal therapy, near infrared (NIR) light-responsive drug release, and rapid clearance of small inorganic particles from the body.

Wide ranges of optical properties are reported including characteristic absorption peak in the visible or NIR ranges, or broadband absorption. It is unclear how the complex interaction among a large number of small gold nanoparticles contribute to the collective optical property of a plasmonic vesicle. In this study, the collective optical properties of plasmonic vesicles are examined and four characteristic regimes, namely the isolated nanoparticle regime, Coulomb interaction regime, black gold regime, and nanoshell regime, are revealed. Small plasmonic nanoparticles need to be very close or weakly overlap to give a broadband absorption (i.e., black gold regime) or form a NIR plasmon peak. Furthermore, smaller gold nanoparticle or larger core size leads to higher NIR peak shift and photothermal conversion efficiency. It is anticipated that this study provides design guidelines and thus have a significant impact on further design and development of complex plasmonic nanostructures and vesicles for biomedical applications.

Acknowledgement:
We acknowledge the grant support from National Science Foundation and CPRIT.

TRACK 1
Nano/micro therapeutics and drug delivery systems

Track Organizer: **Xiaoming He**, *University of Maryland, College Park, MD, United States*
Track Co-Organizer: **Seungpyo Hong**, *University of Wisconsin-Madison, Madison, WI, United States*

1-8
MULTI-PHYSICS OF DRUG AND NANOPARTICLE DELIVERY
Los Angeles, OMNI Hotel, Bradbury Room 10:30am - 11:50am

Session Organizer: **Michelle Digman**, *University of California, Irvine, Irvine, CA, United States*

Passive, visible light-triggered sustained delivery of therapeutically-relevant levels of timolol using engineered contact lenses

Keynote. NEMB2018-6282

Gerard Marriott, *University of California-Berkeley, Berkeley, CA, United States*

Timolol is a non-selective ?-adrenergic receptor antagonist that is used to lower the intraocular pressure (IOP) in patients with glaucoma. Timolol is administered as an eye-drop at >>106 higher than the inhibitory concentration for ?-adrenergic receptors (?ARs). This mode of drug-delivery causes sides effects, including burning-sensations and cardiac dysfunction that account for low patient compliance. Here, we describe a new class of contact lens that delivers a therapeutically-relevant concentration of timolol (~10ki) to the eye on exposure to daylight over a period of at least 10-hours. Timololol is coupled to the hydrogel backbone of the lens via a photo-labile (caged) linker. Exposing the lens to a normal level of indoor sunlight (>>400nm) triggers the photoisomerization of the caged group and release of timolol to the tear-film. Photo-generated timolol applied to the eyes of a mouse model of glaucoma is shown to lower the IOP to the same level as authentic timolol. The daylight-triggered release of therapeutically-relevant levels of timololol from engineered contact lenses would avoid side-effects associated the eye-drop delivery, while related formulations may allow for passive drug-delivery of other small molecule and protein therapeutics to treat other ocular diseases.

Cinnamon (Cinnamomum cassia) Bark Mediated Highly Fluorescent Carbon Dots and its Derivatives for Drug Delivery Applications

Technical Presentation. NEMB2018-6134

Jongsung Kim, Seshadri Reddy Ankireddy, Seong Soo A An, *Gachon University, Seongnam, Korea (Republic)*

Environmentally benign, smart and intelligent nanomaterials are gaining potential interest in the field of nanomedicine and therapeutics. Similarly, highly fluorescent, non-toxic, biocompatible carbon dots have been offering such applications for the last two decades due to their semiconducting and quantum confinement effects with tunable optical properties.

In addition, they possess amazing anticancer properties without any side effects. Herein, we present an easy and simple, highly fluorescent carbon dots (CDs) from Cinnamon bark through one pot synthesis via hydrothermal process. As prepared CDs were highly water dispersible due to polar functional groups such as hydroxyl (-OH), carboxylic (-COOH), and amine (-NH2) on its surface. After that, the surface of the CDs has been modified with anticancer drugs like Pemetrexed, and Gemcitabine (SMCDs) using EDC and NHS sulfo-coupling reaction. As prepared CDs and its derivatives were characterized using various analytical tools such as HRTEM, XRD, XPS, UV-vis, FTIR, Raman, PL and lifetime decay analysis. Moreover, these bare CDs, free drugs were examined thoroughly with the SMCDs against A549 lung cancer cells. Interestingly, enhanced drug performance was observed from SMCDs when compared with the neat drugs and CDs due to the free release of drugs via lysosomal sequestration and rapid distribution into the cytoplasm at low cellular pH conditions. Such simple and environmentally benign fluorescent nanomaterial based strategies can offer applications as excellent nanocarriers to treat cancer and other diseases.

Reaction-Diffusion Kinetics During Selective Photo-Inactivation of Proteins by Molecular Hyperthermia

Technical Presentation. NEMB2018-6203

Daipayan Sarkar, Peiyuan Kang, Steven O. Nielsen*, The University of Texas at Dallas, Richardson, TX, United States*, ***Zhenpeng Qin****, Univ of Texas At Dallas, Richardson, TX, United States*

Understanding protein folding and unfolding has been a long-standing fundamental question and have important applications in manipulating protein activity in biological systems. The rate at which proteins change their structure across a large temperature range plays a crucial role in our fundamental understanding of protein folding/unfolding, the design of novel nanoparticle thermal therapeutics, and selective destruction of protein function. Experimental investigations of protein unfolding have been predominately conducted by small temperature perturbations (e.g. laser-temperature jump), while molecular simulations are limited to small timescales (currently up to microseconds) and high temperatures to observe unfolding. Thus, it remains unclear how fast a protein unfolds across a large temperature range.

Recently, a novel experimental technique, molecular hyperthermia, utilizes nanoscale heating to inactivate targeted proteins by exposure to very high temperatures with ultrashort nanosecond laser pulses. In this work, enabled by molecular hyperthermia, we examine the protein inactivation kinetics at ultra-high temperatures (>> 373 K) by constructing a temperature dependent rate relationship and subsequently connect the rate to the protein unfolding measurements at low temperatures (< 373 K). In doing so we observe the protein unfolding rate is less sensitive to temperature change at the higher temperatures, which significantly departs from the Arrhenius behavior extrapolated from low temperatures. To account for this effect, we propose the use of a reaction-diffusion kinetic rate law that modifies the temperature-dependence of protein unfolding by introducing a diffusion limit. Analysis of the reaction-diffusion model gives general guidelines in the behavior of protein unfolding (reaction-limited, transition zone, and diffusion-limited) across a large temperature range from physiological temperature to extremely high temperatures. We then compare the reaction-diffusion model against the Arrhenius kinetic model extracted from low-temperature experiments, and find that the predictions of the reaction-diffusion model better agree with observations from molecular hyperthermia experiments.

We further demonstrate that the reaction-diffusion model is particularly useful for designing optimal operating conditions for molecular hyperthermia. Specifically, by investigating the optimal combination for gold nanoparticle size, laser energy density and pulse duration, we construct a ?phase-diagram? to determine that increasing the pulse duration from 6 ns to a value in range 50-500 ns can reduce the possibility of gold nanoparticle overheating (i.e. fragmentation) while obtaining nanoscale confined protein inactivation. The experimentally validated reaction-diffusion kinetics of protein unfolding is an important step towards understanding protein-unfolding kinetics over a large temperature range and over a nine-fold timescale. This has important applications including molecular hyperthermia and calls for future studies to examine this model for other protein molecules and serves as a fundamental tool for application of lasers in nanomedicine.

Acknowledgement:
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Nonmonotonic Improvement of Blood Circulation, Tumor Accumulation and Treatment Efficacy for Nanoparticles as the PEG Molecular Weight Changed

Technical Presentation. NEMB2018-6129

Song Shen, Ji-Long Wang, Xiao-Jiao Du, Jun Wang*, South China University of Technology, Guangzhou, China*

Engineering nanoparticles of reasonable surface (polyethylene glycol) PEG lengths is important for designing efficient drug delivery systems. Minimizing the disturbance by other nanoproperties, such as size, PEG density, etc., is crucial for systemically investigating the impact of surface PEG length on the biological behavior of nanoparticles. In the present study, nanoparticles with different surface PEG lengths but similar other nanoproperties were prepared by using poly(ethylene glycol)-block-poly(?-caprolactone) (PEG-b-PCL) copolymers of different molecular weights and incorporating different contents of PCL3500 homopolymer. The pharmacokinetics, biodistribution, cellular uptake and antitumor efficacy of nanoparticles were well studied. The results demonstrated PEG length-dependent changes in the biological behaviors of nanoparticles and exhibited nonmonotonic improvements as the PEG molecular weight increased from 3400 to 8000 Da. Nanoparticles with a surface PEG length of 13.8 nm (MW = 5000 Da) significantly decreased the absorption with serum protein and interaction with macrophage cells, which led to prolonged blood circulation time, enhanced tumor accumulation and improved antitumor efficacy. The present study will help to establish a relatively precise relationship between surface PEG length and the in vivo behavior of nanoparticles.

TRACK 4
Nanomanufacturing and functionalization of biomaterials

Track Organizer: **Song Li***, University of California, Los Angeles, Los Angeles, CA, United States*
Track Co-Organizer: **Hyunjoon Kong***, University of Illinois At Urbana-Champaign, Champaign, IL, United States*

4-4
NANOSTRUCTURED MATERIALS FOR CELL AND TISSUE ENGINEERING
Los Angeles, OMNI Hotel, Crocker Room 10:30am - 11:50am

Session Organizer: **Ali Khademhosseini***, UCLA, Los Angeles, CA, United States*
Session Co-Organizer: **Hyunjoon Kong***, University of Illinois At Urbana-Champaign, Champaign, IL, United States*

Nano- and Microfabricated Hydrogels for Regenerative Engineering

Keynote. NEMB2018-6240

Ali Khademhosseini*, UCLA, Los Angeles, CA, United States*

Engineered materials that integrate advances in polymer chemistry, nanotechnology, and biological sciences have the potential to create powerful medical therapies. Our group aims to engineer tissue regenerative therapies using water-containing polymer networks, called hydrogels, that can regulate cell behavior. Specifically, we have developed photocrosslinkable hybrid hydrogels that combine natural biomolecules with nanoparticles to regulate the chemical, biological, mechanical and electrical properties of gels. These functional scaffolds induce the differentiation of stem cells to desired cell types and direct the formation of vascularized heart or bone tissues. Since tissue function is highly dependent on architecture, we have also used microfabrication methods, such as microfluidics, photolithography, bioprinting, and molding, to regulate the architecture of these materials. We have employed these strategies to generate miniaturized tissues. To create tissue complexity, we have also developed directed assembly techniques to compile small tissue modules into larger constructs. It is anticipated that such approaches will lead to the development of next-generation regenerative therapeutics and biomedical devices.

Development Of Nano-Pillars On The Surface Of Implants Based On Biomimetic Design

Technical Presentation. NEMB2018-6166

Rupak Dua*, Hampden-Sydney College, Chesterfield, VA, United States*, ***Drew Elliott, Brandon Knouse****, Hampden-Sydney College, Hampden-Sydney, VA, United States*

Bacterial infections still possess a great concern in orthopedic and dental implant failure. Infection on implants is associated with bacterial adhesion and subsequently formation of biofilm at the implant site which is resistant to both the immune system and the antibiotics. Previous investigations have been focused on functionalizing the surface of implants with antibiotics to prevent bacterial infections. However, they have demonstrated limited success. Therefore, there is a need to fabricate implants whose surfaces have the inherent ability to kill the bacteria on contact.
We propose to create a smart surface for implants that will inhibit the growth of bacteria on them but allow the mammalian cells to adhere and proliferate on them. In order to accomplish this, we in this study inspired by cicada wing structure, engineered the titanium (Ti) (Grade 5) surface using alkaline hydrothermal treatment (AHT) to create nano-spikes like structure. Surface topology for different groups (Control, 4-Hour AHT & 8-Hour AHT) was assessed through scanning electron microscope (SEM). Effectiveness and mechanism for anti-bacterial properties on the novel surfaces developed were evaluated via commercially available bacterial viability kit and SEM respectively in both static and dynamic environment. In our study, we used Staphylococcus aureus (gram-positive, non-motile), Pseudomonas aeruginosa (gram-negative, motile) and Escherichia coli (gram-negative and motile) bacterial strains.

SEM images of the Ti plates showed unique patterns for each group. Control plates had a relatively smooth surface, with small artifacts on the surface. Ti plates that underwent 4-hour AHT were densely covered with 250 nm spikes and the tip of those nano-spikes was broad and round. 8-Hour AHT plates were densely covered with 900 nm spikes and were more uniformly distributed, thinner, and had a pointed end. We found a significant increase in the number of dead cells on the plates for all 3 strains of bacteria P.aeruginosa, S.aureus & E.coli ($P<0.05$) that underwent AHT treatment when compared with the control plates. The 8-Hour AHT Ti plates were more effective in killing gram-positive and gram-negative bacteria on contact. Results also indicated that there is less adhesion of bacterial cells in the dynamic environment on AHT treated plates.

Nonetheless, in summary, we demonstrated that the nanostructures generated on titanium surface by the hydrothermal treatments show bactericidal properties for both motile and non-motile bacteria. This treatment is also effective not only for gram-positive bacteria but also for gram-negative bacteria which are otherwise very difficult to treat with conventional antibiotic treatment.

Enhanced Incorporation of Acellular Dermal Matrices is due to Platelet Rich Plasma Induced Macrophage Polarization

Technical Presentation. NEMB2018-6207

Jeffrey Van Eps*, Houston Methodist Hospital, Houston, TX, United States*, ***Silvia Minardi****, Northwestern University, Evanston, IL, United States*, ***Xin Wang****, Houston Methodist Research Institute, Houston, TX, United States*, ***Raquel Araujo-Gutierrez, Keith Youker****, Houston Methodist Hospital, Houston, TX, United States*, ***Ennio Tasciotti****, The Methodist Hospital Research Institute, Houston, TX, United States*, ***Joseph Fernandez-Moure****, University of Pennsylvania, Phladelphia, PA, United States*

Introduction: Platelet rich plasma (PRP) has been shown to improve metrics of incorporation (MOI) and reduce recurrence of ventral hernias repaired (VHR) with acellular dermal matrix (ADM). Macrophage phenotype differentiation has also been shown to influence ADM remodeling. We sought to determine the effect of PRP on macrophage polarization in a rat model of VHR with ADM. We hypothesized that PRP would induce a differential pattern of macrophage polarization towards a regenerative phenotype.

Methods: Lewis rats underwent VHR with non-crosslinked ADM 30 days(d) after hernia creation. PRP was applied prior to closure and tissue harvested at 3d and 7d. To determine macrophage phenotype, tissue was decellularized and flow cytometry performed. Expression of inflammatory (M1) genes (IL-1b, iNOS, TNF?) and regenerative (M2) genes (ARG-1, IL-10) were then quantified with RT-PCR. To assess MOI, tissues were fluorescently stained for ?SMA and CD31 and expression of Col1, Col3, VEGF, and vWF quantified by RTPCR .

Results: PRP treated ADMs had increased percentage of M2 (CD206+) macrophages at 3d. This correlated with increased expression of M2 associated genes and decreased expression of M1 associated genes at 3d. PRP treated ADMs showed increased ?SMA and CD31 intensity and increased Col1, Col3, VEGF, and vWF expression at 7d.

Conclusions: PRP induced a differential pattern of macrophage polarization to the M2 phenotype and was associated with improved MOI. These findings suggest that M2 polarization may be responsible for the clinically relevant finding of reduced long-term recurrence demonstrated in our previous studies.

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