Dear Attendee of NEMB2018:

On behalf of the organizers, we would like to welcome you to Los Angeles to the 6th American Society for Mechanical Engineers (ASME) NanoEngineering in Medicine and Biology Conference (NEMB 2018). At this meeting, you will have the opportunity to discuss the most recent advances in nanobiotechnology and nanomedicine with luminaries and pioneers of the field. Whether it’s a tutorial, plenary, keynote and theme presentation, a poster presentation, or a social event, we believe that you will enjoy these exciting elements of the conference. We hope you will benefit from the academic and industrial breadth of the meeting.

Applications of Nanoengineering for medicine and biology are having a dramatic impact on a myriad of healthcare needs, product development and biomedical research. These include nanoparticle-based imaging probes and drug/gene carriers for new and improved disease diagnostics and therapeutics, bio-inspired nanomaterials and nanostructures, and novel Nanoengineering tools for biological and medical applications. These frontiers of engineering, biology and medicine at the micro- and nano-scale will be highlighted at NEMB 2018. In addition, work contributing to completely new fundamental understanding of biological processes and phenomenon at the nanoscale will also be presented. Together these fundamental and applied aspects of the meeting provide the basis for solving grand challenge problems in cancer, infectious disease, cardiovascular, neurological diseases and global health. Nanoengineers and nanoscientists are indeed changing the world and are having a profound impact on medicine and biology!

We would like to acknowledge support for the conference from the National Science Foundation, Purdue University, Washington University at St. Louis, University of California, Irvine, University of Minnesota, and many generous funders acknowledged on our website and in our program. We would also like to acknowledge and highlight the many volunteers who helped assemble the scientific program for this conference especially our Steering Committee (Professors Abe Lee, Bumsoo Han, John Bischof, Guy Genin, Gang Bao), the Tutorial Speakers and Participants, Track Chairs, and Poster Awards committee (led by Zhenpeng Qin and Masaru Rao). You will see that amongst the Plenary and Keynote Speakers, Track Chairs and other attendees many are leading figures in the field. In addition to stimulating scientific and technical discussions, there will be ample opportunities for networking, especially for young researchers to mingle with senior investigators. Showcasing cutting edge research in Nanobioengineering with broad participation constitutes the heart of this meeting, as evident by how the talks, sessions, and tracks are constructed in the technical program. Finally, working hard behind the scenes is a devoted staff of technical assistants from ASME. The latter includes lead organizer extraordinaire Christine Reilley, Program Manager – Kanupriya Parasher and Webtool Coordinator – Laraine Lee.

We wish you a productive and enjoyable stay in Los Angeles. Please stay tuned for information about the next NEMB conference!

Abe Lee
Conference Chair

Bumsoo Han
Technical Program Chair

OMNI Los Angeles Hotel,
California Plaza,
Los Angeles, CA
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-compatible and high-ly-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 high, serum environments. Cytotoxicity of dCNTs was evaluated in several murine and human cell-types, including prostate and melanoma cancer cell lines, as well as normal MSCs. Critically, dCNTs were found not 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 feasibility 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 in 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, Vinip 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 derivatives CTNnols. Particle size analysis, zeta potential, PDI and FE-SEM were also used for characterization of nanconjugate. 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 8 and 4.3 times when compared to pure drug. It was found that the synthesized nanconjugate was hemocompatible and offered low protein binding. All the findings are promising in nature and the nanconjugate 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

**Crystal Alvarez, University of California, Riverside, San Bernardino, CA, United States, Natanael Cuando, Guillermo Aguilar, University Of California, Riverside, Riverside, CA, 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.
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 atomic 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 following 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.

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In this research, a bio-inspired scaffold based on the observed geometrical pattern of theapatite (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.

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

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 increase 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.

Plasmatic 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 (10-120 mg/L) 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 render 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 internal 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, Wonyoung 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 bio-mechanical 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 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 um2/wp 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 applied stress was applied on 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 luminous 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 by 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.
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.

**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 lumened 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,** RadfanQbio, Seoul, Korea (Republic), **Joowon 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.

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.
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.

A kinematic description for the motion of a deformable body that was constructed out of a Gram-Schmidt factorization of the deformation gradient recently developed. 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 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 Sarigol, Georgia Tech, Atlanta, GA, United States

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 QBE T, 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

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

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.

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
The stray field from the magnetic nanoparticles will then be picked up by the sensor, with the magnitude and 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 biosassay 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 nanoparticles 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 biorthogonal click chemistry linkers. Our final antibody-targeted lifetime nanoparticles 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 nanoprobe may be simultaneously deployed for resolving molecular information using only lifetime information.

Signal-amplifying nanoparticle/hydrogel hybrid microstructure biosay for metal-enhanced fluorescence detection of paraaxon
Poster Presentation. NEMB2018-6123

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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 biosassays. 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

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A new metal-enhanced fluorescence-based immunoassay platform was prepared on fibrous substrates. First, polycaprolactone (PCL) fibers were obtained via electrosprinning 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

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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 cannot 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. Different nanoparticle 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 an a-C:H and an AgNP interlayer 3) quasi sandwich films with a base layer of an 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

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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.
Enhanced Alignment of the Neural Stem Cells on the Touch-Spun Nanofibrous Scaffolds
Poster Presentation. NEMB2018-6131

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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 touchspin 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 electrospin and touchspin scaffolds were seeded with NE-4C neuroepithelial cells (NSCs) for biocompatibility evaluation. The highly aligned electrospin and touchspin fibers had fiber diameters of approximately 670 and 700 nm respectively. XRD analysis revealed that peak positions for both electrospin and touchspin PCL fibers were essentially identical, suggesting no change in crystal structure by fabrication techniques. However, the degree of crystallinity of the touchspin fibers was greater than that of electrospin fibers at various spinning rates. Also, the Young’s modulus values of the touchspin fibers at various spinning rates were much higher (>600%) than those of electrospin fibers. NSCs exhibited an elongated neurite growth along the touchspin PCL nanofibers at varying spinning rates, whereas, they tended to aggregate on the entangled electrospin PCL nanofibers. As the spinning rate of the touchspin 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

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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 elderly 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 bienergetic 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

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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 mechanic 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

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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) diacylate (PEGDA) were utilized as the printing ink (GelMA-PEGDA).
Anti-Proliferation of Breast Cancer Cells Regulated by DNA Walkers

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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 released into ECM and diffuse 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 carboclate-terminated polypropyleneimine (PPI) dendron via ligand exchange reactions. Its structure, when demonstrated stable, can be used in the future to attach active targeting moieties 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 (5.2 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 reconstitution 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.

Coated Gold Nanoparticles in PC3 Tumors
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 of the tumors injected with the high 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 conflicting 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 layer, 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 biuda, and diabetes mellitus. The loss of neurological connection with the bladder causes a decrease or loss of sensation of fullness. In turn leads to increase in urine volume stored during filling (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 pre-stretch 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 (i) stretch / stiffness or (ii) collagen, and elastin, and (ii) their phenotype (i.e., contractile vs synthetic) by analyzing the expression of α-caldesmon and alpha smooth muscle actin (75SMA). 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 respond 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 respond 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-norbormene (1.125 w/v%). Gels were exposed upon exposure to UV light (365 nm, 3-5.75 mw/cm2) for 15 s in the presence of a cytocompatible photoinitiator LAP (Lithium Pehnly (2, 4, 6-trimethylbenzoyl) pphosphinate, 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’’), kinetic through the use of 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±100 kPa, 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 differing by various biological 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 pulse lasers 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 UT Dallas.

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 are involved in heating, the temperature 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 Stimulator) 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
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 a barrier. By using picosecond pulsed laser, we generated plasmonic nanobubbles by activating targeted plasmonic nanomaterials. These nanobubbles then acted as a barrier. By using picosecond pulsed laser, we generated plasmonic nanobubbles by activating targeted plasmonic nanomaterials. These nanobubbles then acted as a barrier.

Supported by Funding from Cancer Prevention & Research Institution of Texas (CPRIT)

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 10^7 °C/min. This can be used to treat cancer as has been extensively studied, or more recently to enhance the rewarming of vitrified systems. For instance, low concentration cryoprotective agent (i.e. 2% M CPA) vitrified cells or embryos require fast rates of warming compared with traditional convective warming to survive the warming. 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.
Microfluidics-based immunoaffinity studies were carried out by using a herringbone-microchannel 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 Rooholghodas, 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 populations 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, efficient 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, 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 fluid 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 warming) 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 re-warming 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 diffusion measurement at -173C confirmed the amorphous state of the droplets. We have also developed a modified? cryoscoop? To transfer the droplets under laser for re-warming. 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(pyrolrrole) 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(pyrolrrole) 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, Petyuan 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? 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 stimulus 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 Acellar 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, Philadelphia, PA, United States

Introduction: Platelet rich plasma (PRP) has been shown to improve incorporation and reduce CD6+ 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 CD6+ cell infiltration in a rat model of VHR. We hypothesized that increasing concentration of PRP would lead to improved incorporation and decreased CD6+ 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/ml (LOW-plt), 1x106plt/ml (MID-plt), or 1x107plt/ml (HIGH-plt) and tissue harvested at 2 and 4wks. Cellularization, tissue deposition, and tissue regeneration 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 CD6+ 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

Jember 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 \( d_{\text{gap}} \), and particles larger than the \( d_{\text{gap}} \) are trapped within the vortex. The equation for the \( d_{\text{gap}} \) is as follows: 
\[
\text{d}_{\text{gap}} = \left( \frac{U_b}{U_s} \right) \frac{W}{2},
\]
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 \( d_{\text{gap}} \), 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 the 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 downregulate the immune response.

Artificial antigen presenting cells (aAPC) have emerged as an effective way to modulate the immune response. 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 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-\( \gamma \) and TGF-\( \beta \) 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.
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 cyrobiology 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 micromachined techniques for genetic modification. 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).

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.

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

Nanomedicine approaches to improve cancer immunotherapy

Keynote. NEMB2018-6141

We outline preliminary efforts to develop a new form of microinjection using silicon micromachining. 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.

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

Hesam Babahosseini, Tom Misteii, 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 microfluidics 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 Segalinny, Xiaoming Chen, Lingshun Kong, Cl 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
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 complicated 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 these 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.

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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.
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-CA09338.

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

Jyyoon Bu, Yun Hwa Choi, Sin-Jung Park, 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(amicodamine) (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 multivalant binding effect.

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, tissue 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.

Enhanced PD-1/PD-L1 Binding Kinetics via Dendrimer-mediated Multivalant Binding Effect
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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.

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. 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

Nicolle 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 μm 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 PCLmicrofibrous 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

Zubaher 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 remains 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 yield-e 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 integrinα5s and its spatial distribution. These qualitative results will provide the direction for local stiffness influence in the neuronal behavior.
Additional images and text:

**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 Ehhtyatkhar, Hype 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 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 nanoprobes 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.
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

Colonctal 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 10^3 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 imperfect 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, 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, 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 phenomena. Specifically, the electric double layer - the ion layer that arises based on the surface-liquid 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 channel 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 nano-fluidic-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/limited 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 Engineering, 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 immense 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 by a factor of 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 largescale nanomanufacturing. Additionally, scaling-up the AMF system’s 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 up to 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, temperature, bioheat transfer) (b) end-points defining clinical efficacy ? tumor destruction vs organ viability (c) constraints/ flexibility in the driving AMF conditions ? Adkinson 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 faceted 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, Cy-OPF, mCypFP, 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 plasmionic gold-coated liposomes, or plasmionic 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 trisphosphate (IP3), in both an immobilized cell line and primary neurons.

To overcome the limited penetration of light into brain tissue, we investigated gold-coated mechanoresponsive 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 neuropeptides. 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 Immunono-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 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. We will use 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

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\textsuperscript{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\textsuperscript{i} response with FAK activation, whereas a high degree of Piezo1 activation (sustained mode) causes a sustained Ca\textsuperscript{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\textsuperscript{i} response and a FAK activation.

**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 Engineering, 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 towards the ovules, and the mating of fungi. Experimental systems that bring together a population of mating type A and B 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 chemotropically signaling between populations of mating type A and B yeast cells with spatiotemporal programmability and sensitivity that were revealed with biofabrication in a microfluidic device. Free-standing 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 post 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 B cells populations in the micrometer length scale: the cells either proliferated, developed a stereotypical polarized projection termed a shmoo or 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 Foley**, 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-assemblies of embedded enzymatic cells and/or nanotube 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 allows 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 microliter 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 BIOSENORS 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 testing. 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). 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

Hyelin Shin, Hyeonaag 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 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 3-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(carboxyethyl)phosphine (TCEP) to allow rapid interactions with spherical gold nanoparticles. Here, we show that TCEP can also act as a powerful oxidant on flat gold nanoparticles 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 nanoparticles (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, with 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 Immunassays**

NEMB2018-6140

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 testing. 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). The basic design of the device a colorimetric visual detection platform based on the integration of nanozyme and immunoassay.
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 10-1000 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.
The technique has been used to measure and image with both plasmids and proteins into the cytoplasm or the nucleus of living cells. The extraction and quantify material from living cells. mRNA and micro RNA expression SPM probes to create local dielectrophoretic forces and have used these forces to 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 plasmas 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.

Jiyoon Bu, 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 historically 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(amoidoamine) 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 silicon-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 convective in ocular drug delivery

Technical Presentation. NEMB2018-6241

Anita Penkova, University 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.

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

Session Organizer: Milos Marinkovic, Biopact, Austin, TX, United States
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 diffractometry, 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.

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 spectroscopy, 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 cardiomyocytes 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 myofibrillogenesis 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 Politècnica 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 mechanics of gene function. However, intranuclear mechanics (e.g. stiffness of subnuclear domains) is not well understood, in part due to technical challenges of measurement inside the cell. 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 epifluorescence 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 minimized 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 Poisson’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 nuclear 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 stretch 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 Jean, 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**
Collagen is a pervasive, extracellular matrix (ECM) protein. From skin and bones to blood vessels 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 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

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.

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

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 miRNA, 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.
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 pulsed 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 microvascular 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 electrophoresis above ~1000V/cm and no significant disruption occurs below ~300V/cm. Our results provide a 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 Leon-Plata, Magdalena Szymusiak, Pin Zhang, University of Illinois at Chicago, Chicago, IL, United States, Thomas Irving, Welfang Shang, Illinois Institute of Technology, Chicago, IL, United States, Sagar Kathuria, Osman Bilsel, University of Massachusetts Medical School, Worcester, MA, United States, Ying Liu, UNIVERSITY OF ILLINOIS AT 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 were studied. Nuclearation, merging, and insertion, were observed. Understanding the kinetics of nanoparticle formation will provide important guidance, which is not available currently, for designing and optimizing nanostructure with a wide spectrum of applications.
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 insights into VIC 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 AV-ECM mechanical coupling at receptor level under various pathophysiological conditions and the investigation of possible treatment strategies targeting the myofibroblast phenotype characteristic of early signs of valvular disease.

The field of interest is in disease control such as detecting earlier stages of cancer (prostate cancer, colon cancer, and pancreatic cancer) and trace amount of contagious pathogens (pathogenic virus and bacteria) via nanotechnological approaches. 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 methods require expensive equipment and limited materials for the printing. On the other hand, NFE is a low-cost fabrication technique and can be used in bio-compatible 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 μm and the spacing of 20 μm 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 to moments of trauma. Our approaches involve an ultrasonic transducer and biocompatible Polyacrylate (PCL) microbubbles. 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 1.67MHz transducer. Using a 100kHz 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.

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 resolve 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.
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 antioxidizing 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

**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 multi-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.

**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, 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, Praneet Pairs, Yi bo 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, 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
Adsortion Behavior of Bone Morphogenetic Protein (BMP-2) on Nanoscale Topographies

Technical Presentation. NEMB2018-6265

Izabela Marqueti, North Carolina A&T State University, Greensboro, NC, United States, Salii 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 patterned 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 bacteria 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 microfluidic 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.
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 anatomic 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 University, Columbus, OH, United States, Jonathan W. Song, Ohio State University, Columbus, OH, United States, Carlos E. Castro, Ohio State University, 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.

References:

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 was magA, which codes for a protein that acts as an iron transporter. When expressed in 293T 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 293T 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.

References:
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 Autónoma 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 immunotherapeutically 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.
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 cell lines such as adipogenic, osteogenic, and chondrogenic. The commitment of a cell to differentiate into a particular lineage is regulated by the interplay 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 differentiation. 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 secretomere 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 addition 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 aipogenesis 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-microparticles that can efficiently contain and release these molecules upon demand. Pre-fabricated, differentiation factor-carrying microparticles will then be strategically placed along with the cells and scaffolds during printing. Plasmionic gold-nanorods incorporated in the polymer-layer enable rupture of the shell on demand using a laser, in order to release the differentiation factors. These microparticles 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-studded microparticles with aqueous cores are formed.

While water-soluble differentiators can be directly dissolved in the aqueous core, liposoluble differentiators (such as IW2 that is required to achieve cardiomyocytes) passively leaks out of the organic phase of the microparticle, 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. 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

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. Polyurethane 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 patterned myotubes followed the linear morphology of the muscle cells. We confirmed the NMJ formation by immunofluorescently using neurolament, 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

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 DNAzymes 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.

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-WMSNs nanoparticles in the context of extracellular acidic pH was confirmed using propidium 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 (polydispersity, nonhomogeneous 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 transferferrin 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 monopore dispersive solution. As the nanoparticle size grows beyond 16 nm, this effect dies away and aggregation leads to less photothermal 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.

References:

**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 with 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.

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**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 NANOPIRATE 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 β-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 β-adrenergic receptors (βARs). 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. Timolol 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 timolol 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 Anikreddy, 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), carboxyl (-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 fluoroscent 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 rates is less sensitive to temperature changing at these higher temperatures, which significantly depart 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:** The authors acknowledge the startup support provided to Z.Q. by Department of Mechanical Engineering, The University of Texas at Dallas.

**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 systematically 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(γ-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 therapies 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 Arauco-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, Philadelphia, 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.
Dear Attendee of NEMB2018:

On behalf of the organizers, we would like to welcome you to Los Angeles to the 6th American Society for Mechanical Engineers (ASME) NanoEngineering in Medicine and Biology Conference (NEMB 2018). At this meeting, you will have the opportunity to discuss the most recent advances in nanobiotechnology and nanomedicine with luminaries and pioneers of the field. Whether it’s a tutorial, plenary, keynote and theme presentation, a poster presentation, or a social event, we believe that you will enjoy these exciting elements of the conference. We hope you will benefit from the academic and industrial breadth of the meeting.

Applications of Nanoengineering for medicine and biology are having a dramatic impact on a myriad of healthcare needs, product development and biomedical research. These include nanoparticle-based imaging probes and drug/gene carriers for new and improved disease diagnostics and therapeutics, bio-inspired nanomaterials and nanostructures, and novel Nanoengineering tools for biological and medical applications. These frontiers of engineering, biology and medicine at the micro- and nano-scale will be highlighted at NEMB 2018. In addition, work contributing to completely new fundamental understanding of biological processes and phenomenon at the nanoscale will also be presented. Together these fundamental and applied aspects of the meeting provide the basis for solving grand challenge problems in cancer, infectious disease, cardiovascular, neurological diseases and global health. Nanoengineers and nanoscientists are indeed changing the world and are having a profound impact on medicine and biology!

We would like to acknowledge support for the conference from the National Science Foundation, Purdue University, Washington University at St. Louis, University of California, Irvine, University of Minnesota, and many generous funders acknowledged on our website and in our program. We would also like to acknowledge and highlight the many volunteers who helped assemble the scientific program for this conference especially our Steering Committee (Professors Abe Lee, Bumsoo Han, John Bischof, Guy Genin, Gang Bao), the Tutorial Speakers and Participants, Track Chairs, and Poster Awards committee (led by Zhenpeng Qin and Masaru Rao). You will see that amongst the Plenary and Keynote Speakers, Track Chairs and other attendees many are leading figures in the field. In addition to stimulating scientific and technical discussions, there will be ample opportunities for networking, especially for young researchers to mingle with senior investigators. Showcasing cutting edge research in Nanobioengineering with broad participation constitutes the heart of this meeting, as evident by how the talks, sessions, and tracks are constructed in the technical program. Finally, working hard behind the scenes is a devoted staff of technical assistants from ASME. The latter includes lead organizer extraordinaire Christine Reilley, Program Manager – Kanupriya Parasher and Webtool Coordinator – Laraine Lee.

We wish you a productive and enjoyable stay in Los Angeles. Please stay tuned for information about the next NEMB conference!

Abe Lee
Conference Chair

Bumsoo Han
Technical Program Chair

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