

SYMPOSIUM BM05

Advanced Manufacturing Technologies for Emulating Biological Tissues
November 26 - November 29, 2018

Symposium Organizers

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* Invited Paper

SESSION BM05.02: Bioprinting Strategies for Tissue Modeling
Session Chairs: Akhilesh Gaharwar and Mario Álvarez
Monday Afternoon, November 26, 2018
Sheraton, 2nd Floor, Liberty C

1:30 PM *BM05.02.01

Chaotic Printing—Using Chaos to Fabricate Densely Packed Micro- and Nanostructure at High Resolution and Speed Grissel Trujillo-de Santiago^{1,2}, Maria Díaz-de León Derby^{1,2}, Carolina Chávez-Madero^{1,2}, Mohamadmahdi Samandari^{3,4}, Christian Carlos Mendoza-Buenostro², Gyan Prakash⁵, Sara Cristine Pedroza-González¹, Brenda Giselle Flores-Garza¹, Rute Fabiana Martins-Fernandes², Yu Shrike Zhang⁵ and Mario M. Álvarez¹; ¹Centro de Biotecnología-FEMSA, Tecnológico de Monterrey, Nuevo León, Mexico; ²Departamento de Mecatrónica e Ingeniería Eléctrica, Tecnológico de Monterrey, Nuevo León, Mexico; ³Imperial College London, London, United Kingdom; ⁴School of Mechanical Engineering, College of Engineering, University of Tehran, Tehran, Iran (the Islamic Republic of); ⁵Department of Engineering in Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, Massachusetts, United States.

Nature generates densely packed micro- and nanostructures to enable key functionalities in cells, tissues, and other materials. Current fabrication techniques, due to limitations in resolution and speed, are far less effective at creating microstructure. Yet, the development of extensive amounts of surface area per unit of volume will enable applications and manufacturing strategies not possible today. Here, we introduce chaotic printing—the use of chaotic flows for rapid generation of complex, high-resolution microstructures.

Here we use two classic mixing systems as models, the Journal Bearing (JB) Flow and the Kenics mixer, to demonstrate the use of chaotic printing. In a miniaturized JB flow (miniJB) we induced deterministic chaotic flows in viscous liquids. These flows deform an “ink” (i.e., a drop of a miscible liquid, fluorescent beads, or cells) at an exponential rate to render a densely packed lamellar microstructure that is then preserved by curing or photocrosslinking. In a continuous version of chaotic printing, we created chaotic flows by coextruding two streams of alginate (two inks) through a printing head that contains an on-line miniaturized Kenics static mixer with multiple mixing elements (or sections). In this way, we continuously 3D-print multi-material lamellar structures with different degrees of surface area (as a function of the number of elements used) and full spatial control of the internal microstructure. The combined outlet stream is then submerged in a calcium chloride solution in order to crosslink the emerging alginate fibers and preserve the microstructure.

We show that the exponentially fast creation of fine microstructure achievable through chaotic printing exceeds the limits of resolution and speed of the currently available 3D printing techniques. Moreover, we show that the architecture of the microstructure to be created with chaotic printing can be predicted using computational fluid dynamic (CFD) techniques.

We present different proof-of-principle applications for this technology, including the development of densely packed biocatalytic surfaces and highly complex multi-lamellar and multi-component tissue-like structures for biomedical applications.

2:00 PM BM05.02.02

3D Bioprinted Mini-Brains as a Novel Tool to Study the Glioblastoma Microenvironment Marcel A. Heinrich¹, Ruchi Bansal¹, Yu Shrike Zhang^{2,3,4}, Raymond Schiffelers⁵ and Jai Prakash¹; ¹Department of Biomaterials Science & Technology, University of Twente, Enschede, Netherlands; ²Division of Engineering in Medicine, Harvard Medical School, Brigham & Women's Hospital, Cambridge, Massachusetts, United States; ³Division of Health Sciences & Technology, Harvard-Massachusetts Institute of Technology, Cambridge, Massachusetts, United States; ⁴Wyss Institute for Biologically Inspired Engineering, Harvard University, Cambridge, Massachusetts, United States; ⁵Department of Clinical Chemistry and Hematology, University Medical Center Utrecht, Utrecht, Netherlands.

Glioblastoma-associated macrophages (GAMs) play a crucial role in the progression and invasiveness of glioblastoma multiforme (GBM), however, the exact crosstalk between GAMs and glioblastoma cells is not fully understood. Furthermore, there is lack of relevant in vitro models to mimic their specific interaction in a dynamic and relevant environment. 3D bioprinting offers a promising approach to culture cells with well-defined structure and composition. In this study, we aim to develop novel bioprinted mini-brains that display in vivo-like behavior of both glioblastoma cells and GAMs.

We bioprinted mini-brains (WxLxH; 4x6x3mm) comprised of either glioblastoma cells or macrophages or together to study their interaction in a realistic way. Both macrophages and glioblastoma cells remained viable in the mini-brains for at least 10 days. We observed an induction of glioblastoma-specific markers (e.g. Gfap up to 15-fold) compared to 2D cultures at mRNA level. Next, we studied whether tumor cells recruit macrophages to their site. To

mimic that, we bioprinted mini-brains consisting of either macrophages or glioblastoma cells and cultured them in the same well. We found a 125-fold upregulation of Ccl2, a chemokine related to macrophages recruitment compared to 2D culture, indicating that tumor cells actively recruit macrophages in the 3D co-culture. Furthermore, we cultured mini-brains consisting of macrophages next to glioblastoma cells to confirm their migration. We found that macrophages significantly migrated towards the tumor site, indicating successful crosstalk between these cells. Next, we investigated the effect of direct cell-to-cell contact of tumor cells and macrophages in the 3D culture. We bioprinted mini-brains consisting of macrophages including a cavity containing glioblastoma cells mimicking the clinical situation. We investigated the gene expression of GAM-specific markers and observed a significant upregulation of markers for the GAM phenotype (Arg-1, Mmp2, Mmp9, Cd206), indicating that tumor cells polarized macrophages towards GAMs. In addition, by resecting the tumor area from the mini-brains and investigate the expression of glioblastoma-related markers, we found that markers for tumor progression (Gfap, Chil1) and tumor invasion (Mmp9, Vimentin) were significantly overexpressed in the co-culture, displaying how GAMs support glioblastoma progression and invasion. To examine the clinical relevance of this model, we performed transcriptomic analysis of 159 GBM patients using available database, which showed a significant upregulation of highly relevant markers such as Mmp2, Mmp9 or Chil1. These data indicate that tumor cells induce recruitment of macrophages towards themselves and change their phenotype, as well as how GAMs support tumor progression and invasion. Altogether, our bioprinted mini-brains are a viable tool to study the interactions between different cell types and could potentially be used for drug screening purposes.

2:15 PM BM05.02.03

Tailoring a Functional Microbiotic Consortium via 3D Printing Sudeep Joshi and Manu S. Mannoors; Stevens Institute of Technology, Hoboken, New Jersey, United States.

A characteristically well-diverse assemblage of myriad micro-organisms operating in a synergic environment, constitutes a microbiotic consortium. It possesses a complex spatial and temporal microbial arrangement, which is self-sustained and perform multitudinous task by effective communicative functionality. The ability to custom-tailor a well-diversified microbiotic consortia permitting re-programmability of the microbial composition possess potential application prospects in bacteriology, drug-screening, clinical diagnostics, and therapeutic purposes. Additive manufacturing technique accomplished via 3D printing can serve as an efficient tool to realize such a functional microbiotic consortia.

In the present article, we have utilized 3D printing technique to custom-tailor different genera of cyanobacterial cells within biofriendly hydrogel materials to realize a living microbiotic consortium. Moreover, these cyanobacterial colonies were seamlessly merged with abiotic nanomaterials for creating a functional microbiota capable of photosynthetic energy generation. Specifically, we demonstrate 3-dimensional interweaving of 2 genera of cyanobacteria (*Anabaena* and *Nostoc Sp.*) pre-seeded in a hydrogel matrix with electronic nanomaterial (graphene nanoribbons, GNRs) into various complex spatial geometries to enable harvesting of photosynthetic bio-electrons. Fluorescence and scanning electron microscopic studies were performed to examine the spatial distribution of cyanobacterial cells and their interaction with GNRs, respectively. Photo-electrochemical studies verified highly-conducting GNRs helped in efficient transfer of bio-electrons generated due to the water-splitting reaction during photosynthesis. UV-visible spectroscopy and standard plate counting methods were used to determine the growth of cyanobacterial cells in microbiotic consortium, hence confirming the cytocompatibility of hydrogel matrix. Significantly, the proposed 3D-printing strategy can organize cyanobacteria in complex arrangements to investigate the influence of spatial and environmental parameters in social behaviors for creating photosynthetically active microbiotic consortia.

Techniques developed in this research can also be extended to 3D print other genera of bacterial species with smart hydrogel materials to determine mutualistic relationships between bacteria, designing of synthetic organisms, and post-biotic products. Taken together, our experimental efforts lead towards the better comprehension and understanding of complex microbial arrangement and associated functionality of a robust microbiota.

2:30 PM BM05.02.04

Numerical Simulation of Inkjet and Extrusion Bioprinting—Role of Resolution Amir K. K. Miri¹ and Iman Mirzaee²; ¹Rowan University, Glassboro, New Jersey, United States; ²Mechanical Engineering, University of Massachusetts Lowell, Lowell, Massachusetts, United States.

Since the emergence of the technology, 3D bioprinting has been applied to many areas of biomedicine such as creating customized devices, flexible bioelectronics, and scaffolds for tissue regeneration, novel therapeutic systems, prosthetics, and orthodontics. The macro-architecture of the generated construct can be as complex as the anatomical feature of the desired tissue, which necessitates proper printing fidelity. Printing resolution depends on the technical specifications of bioprinters and the physical properties of bioinks. In this work, a numerical model based on the method of volume of fluid (VOF) was created to obtain some insights on the droplet generation in inkjet bioprinting. Our simulations revealed the spatial and temporal features of the droplets before they impact the substrate, which is highly difficult to observe through experiments. The results further showed that high hydrophobicity of the substrate yielded a better printing resolution and lower stability for bioprinting. We then simulated the process of deposition from a sub-millimeter sized nozzle in extrusion bioprinting. In contrast to inkjet printing, the viscosity was found to be a dominant factor for flow properties inside the nozzle and after deposition. The viscosity dependency of shear rates also affects the surface deformation of the bioink when it leaves the nozzle and the combination of flow-induced stresses with surface tension forces dictates the form of the spherical residue formation. Based on our simulations, by selecting proper bioink properties, the resolution can be improved significantly in extrusion and inkjet bioprinting techniques.

2:45 PM BREAK

3:15 PM *BM05.02.05

Bioengineering Female Reproductive Tract Tissues Monica M. Laronda^{1, 2}; ¹Stanley Manne Children's Research Institute, Ann & Robert H Lurie Children's Hospital, Chicago, Illinois, United States; ²Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, United States.

Hormones produced by the ovary support reproductive tract development and function, and are important for systemic health. The additional systems that are supported include brain, bone and cardiovascular tissues. There is a great need for mimics that represent the dynamic functionality of reproductive tissues in order to improve our understanding of normal function, function affected by disease or disease treatments and to improve current options for our patients. This includes restoring fertility and hormone function for survivors of childhood cancer who develop premature ovarian failure following their life-saving treatments. This particular population would benefit from hormone restoration in addition to new options for preserving and restoring gametes for future biological offspring, as they transition through puberty and may be put at significant risk of co-morbidities without normal ovarian hormones. The female reproductive tract is uniquely different from most model organisms and has forced researchers to develop creative ways to study the human condition. We have turned to engineering solutions to facilitate our quest for answers to these biological problems. This includes using new biomaterials or tissue reconstructed tissues to recapitulate normal female reproductive tract organs, simulating the paracrine and endocrine crosstalk that occurs among these tissues in a microfluidics system and 3D printing scaffolds to engineer follicle support in a bioprosthetic ovary that restored fertility and hormone function in sterilized mice. We continue to make improvements with these systems to impact reproductive biology research and fertility and hormone restoration for patients.

3:45 PM *BM05.02.06

3-D Bio-Printed Glioblastoma-Vascular Niche [Guohao Dai](#); Northeastern University, Boston, Massachusetts, United States.

Glioblastoma (GBM), the most malignant brain cancer, remains deadly despite wide-margin surgical resection and concurrent chemo- & radiation therapies. Two pathological hallmarks of GBM are diffusive invasion along brain vasculature, and presence of therapy-resistant tumor initiating stem cells. Deconstructing the underlying mechanisms of GBM-vascular interaction may add a new therapeutic direction to curtail GBM progression. However, the lack of proper 3D models that recapitulate GBM hallmarks restricts investigating cell-cell/cell-molecular interactions in tumor microenvironments. In this study, we created GBM-vascular niche models through 3D bioprinting containing patient-derived glioma stem cells (GSCs), human brain microvascular endothelial cells (hBMVECs) cells, pericytes, astrocytes and various hydrogels to model glioma/endothelial cell-cell interactions in 3D. Three GBM-vascular models were designed: Model A with large vessels and GBM spheroid; Model B with large- and micro-vessels, and GBM spheroid; Model C with large- and micro-vessels and dispersed GBM cells. Large channels were created by sacrificial 3D bioprinting. Microvessel network was formed through self-assembly of ECs and mural cells (fibroblast, pericytes, and/or astrocytes). Three GBM cell types were used in the study: SD02 and SD03 are GSCs; U87MG is a commercially-available GBM cell line. GSCs cultured in these models maintained stemness and heterogeneity during the long-term cultures. In Model A, GSCs actively invaded into the surrounding tissues (~Day26), initially regressed in response to the drug (~Day50), then developed therapeutic resistance and resumed aggressive invasion (~Day57). In Model B and C, three GBM types presented distinctive invasion patterns and EC-interactions. SD02 cells showed a spiky invasion pattern with elongated morphology. SD03 cells showed a more dispersed invasion pattern with many single cell migrations towards surrounding microvessels. U87MG cells showed a blunt invasion pattern, caused EC death in the spheroid form. In summary we have created GBM-vascular niche models that can recapitulate various GBM characteristics such as cancer stemness, tumor type-specific invasion patterns, and drug responses with therapeutic resistance. Our models have a great potential in investigating patient-specific tumor behaviors under chemo-/radio-therapy conditions and consequentially helping to tailor personalized treatment strategy. The model platform is capable of modifying multiples variables including ECMs, cell types, vascular structures, and dynamic culture condition. Thus, it can be adapted to other biological systems and serve as a valuable tool for generating customized tumor microenvironments.

4:15 PM BM05.02.07

Development of Strong and Biostable Nanocomposite Hydrogels Through Embedded Freeform 3D Printing Coupled with *In Situ* Precipitation [Shengyang Chen](#), Tae-Sik Jang, Matthew Pan and Juha Song; Nanyang Technological University, Singapore, Singapore.

Embedded freeform 3D printing is an emerging 3D printing technique, where a hydrogel-based viscous medium provides support for extruded ink filaments during the printing process, allowing for omnidirectional printing of soft materials. One of the advantages of printing in a support bath is that the composition of the liquid medium can be modified to induce various chemical reactions in printed objects for solidification or functionalization of extruded ink filaments. Herein, we introduced a hybridization process to a 3D freeform printing system to achieve the direct fabrication of nanoparticle-reinforced composite hydrogels. In most composite hydrogel 3D printing systems, particles are preloaded in the ink prior to printing, which often reduces the printability of composite ink with little mechanical improvement due to poor particle-hydrogel interaction of physical mixing. In contrast, the *in-situ* incorporation of nanoparticles into a hydrogel during 3D printing achieves uniform distribution of particles with remarkable mechanical reinforcement, while precursors dissolved in inks do not influence the rheological behavior of pure ink materials. Therefore, we successfully fabricated hyaluronic acid (HAc)-calcium phosphate (CaP) nanocomposite scaffolds through 3D freeform printing of HAc, coupled with *in-situ* precipitation of CaP. Phosphate ions were dissolved in the hydrogel ink and calcium ions were added to the support bath for inducing the *in-situ* precipitation during 3D printing. The composite hydrogels demonstrated a significant improvement in mechanical strength, biostability as well as biological performance compared to pure HAc. Moreover, multi-material printing of composites of different CaP content was achieved by adjusting the ionic concentration of inks. Our method greatly accelerates the 3D printing of various functional or hybridized materials with complex geometries via the design and modification of printing materials coupled with *in situ* post-printing functionalization and hybridization in reactive viscoplastic matrices.

4:30 PM BM05.02.08

The Age of Applications for Bioprinting [Ricky Solorzano](#); Allevi, Philadelphia, Pennsylvania, United States.

In an era where bioprinting continues to hold promise sometimes its hard to understand why and how are they useful. What key applications will allow me to take my research to the next level and stay on the cutting edge. Come and listen to the key ways bioprinting is being most commonly used by researchers around the world.

4:45 PM BM05.02.09

Nanoengineered Inks for 3D Bioprinting [Akhilesh K. Gaharwar](#); Texas A&M University, College Station, Texas, United States.

3D bioprinting is emerging as a promising method for rapid fabrication of biomimetic cell-laden constructs for tissue engineering. However, 3D bioprinting has hit a bottleneck in progress due to the lack of available bioinks with high printability, mechanical strength, and biocompatibility. We have developed multiple approaches to design highly printable bioink for fabricating large scale, cell-laden, bioactive scaffolds. Specifically, we have introduced a family of bioinks including nanocomposite reinforcement, ionic-covalent entanglement (ICE), and nanoengineered ICE (NICE) based bioinks with excellent printability, mechanical properties, and shape-fidelity. These bioinks follow Herschel-Bulkley flow behavior, that shields encapsulated cells from excessive shear stresses during extrusion. The encapsulated cells readily proliferate and maintain high cell viability over 120 days within the 3D-printed structure, which is vital for long-term tissue regeneration. The unique aspect of these bioink is its ability to print much taller and higher-aspect ratio- structures than conventional bioinks without requiring secondary supports. We envision that these new family of bioinks can be used to bioprint complex, large-scale, cell-laden constructs for tissue engineering with high structural fidelity and mechanical stiffness for applications in custom bioprinted scaffolds and tissue engineered implants.

SESSION BM05.01: Biofabrication for Tissue Modeling
Session Chairs: Su Ryon Shin and Weijia Zhang
Monday Morning, November 26, 2018
Sheraton, 2nd Floor, Liberty C

8:00 AM *BM05.01.01

***In Vitro* 3D Tissue Construction by Microtissue Assembly** [Shoji Takeuchi](#); Univ of Tokyo, Tokyo, Japan.

In this presentation, I will talk about several Microfluidic-based approaches for the rapid construction of 3D cellular construct. Large-scale 3D tissue architectures that mimic microscopic tissue structures *in vivo* are very important for not only in tissue engineering but also drug development without animal experiments. We demonstrated a method of 3D tissue construction by using point, line and plane-type microtissues as cellular building blocks. For example, to prepare the point type building blocks, we used an axisymmetric flow focusing device (AFFD) that allows us to encapsulate cells within monodisperse collagen beads. By molding these cell beads into a 3D chamber and incubating them, we successfully obtained complicated and milli-sized 3D cellular constructs. As the line type building blocks, a cell-encapsulating core-shell hydrogel fiber was produced in a double coaxial laminar flow microfluidic device. When with myocytes, endothelial, and nerve cells, they showed the contractile motion of the myocyte cell fiber, the tube formation of the endothelial cell fibers and the synaptic connections of the nerve cell fiber, respectively. By reeling, weaving and folding the fibers using microfluidic handling, higher-order assembly of fiber-shaped 3D cellular constructs can be performed. Moreover, the fiber encapsulating beta-cells is used for the implantation of diabetic mice, and succeeded in normalizing the blood glucose level.

8:30 AM BM05.01.02

Manufacturing Biomimetic Tissue Construct for Regenerative Medicine and Organ-on-a-Chip Application [SuRyon Shin](#); The Brigham and Womens Hospital, Inc, Harvard Medical School, Cambridge, Massachusetts, United States.

Tissue engineering holds great promise as an alternative therapy by creating functional tissue constructs that can reestablish the structure and function of injured tissue. However, a major challenge in tissue engineering is recapitulating the *in vitro*, three-dimensional (3D) hierarchical microarchitecture comprised of multiple cell types and the extracellular matrix (ECM) components of native tissues, along with achievement of continuous function and viability of engineered tissues after implantation. Specifically, survival of implanted cell-laden scaffolds is fully dependent on the oxygenation derived by its connection to blood circulation of the host body. The physiological process of angiogenesis is time-consuming, which results in the failure of clinically sized implants due to starvation-induced cell death, especially in thick and large constructs. Therefore, the incorporation of functional vasculature is important for maintaining thick and large complex tissue constructs, particularly in cardiac and skeletal muscle tissues that require highly vascularized networks to support the large metabolically activity in muscle cells. To address these challenges, 3D bioprinting is emerging as a powerful technique for the development of highly organized and complex 3D constructs. To achieve *in vivo*-like biological functions in 3D tissue constructs, ECM-based biomaterials are required to mimic biological and physical properties that will enhance the resulting tissue function. Furthermore, the bioprinted 3D tissue constructs can be used for toxicity assays based on organs-on-a-chip platforms, which have become increasingly important for drug discovery. The organs-on-a-chip system allows for the testing of cytotoxic effects of pharmaceutical compounds and nanomaterials on physiologically relevant human tissue models prior to moving forward with animal testing or clinical trials. To successfully establish organs-on-a-chip platforms, it is important to monitor the dynamic behaviors of human organ models interacting with drugs *in situ* for a long time. Furthermore, efficient methods for accurate analysis of the dynamic behaviors of human organ models are in urgent demand for improving the effectiveness of clinical predictions of human disease responses to different therapeutics. We introduce a microfluidic, label-free, biosensing technology combined with a 3D bioprinted human organ-on-a-chip system, which jointly allows for long-term and accurate measurements of the concentrations of the biomarkers secreted by tissues in response to drugs. The electrochemical biosensing chip will demonstrate a capability for regenerating its sensor surface, allowing for continual kinetic studies over extended periods of time. We believe that this novel platform technology may be further extended to a wide variety of applications in academia and pharmaceuticals for personalized screenings of drug toxicity, efficacy, and pharmacokinetics in the future.

8:45 AM BM05.01.03

Applications of Multiphoton Polymerized Bio-Functional Platforms [Bianca Buchegger](#)¹, [Johannes Kreutzer](#)¹, [Richard Wollhofen](#)¹, [Jaroslav Jacak](#)^{1,2} and [Thomas A. Klar](#)¹; ¹Johannes Kepler Universität Linz, Linz, Austria; ²Upper Austria University of Applied Sciences, Linz, Austria.

Multiphoton polymerization (MPP) allows fabrication of arbitrary polymer structures in three dimensions with minimum feature sizes down to 100 nm and a lateral resolution around 200 nm. An excitation laser is focused into a photoresist consisting of a highly crosslinking acrylate and a photo-initiator. Adding a second laser beam which induces stimulated emission depletion (STED) of the photo-initiator in the outer rim of the excitation point spread function allows writing of even smaller structures with feature sizes below the diffraction limit.

Including functional groups other than the acrylate groups increases the versatility of the polymer structures, specifically for bio-functionalization. This can be either achieved by mixing of metal-oxo-clusters into the photoresist [1] or by using acrylate monomers with different functional rest groups such as thiols or carboxy groups enabling orthogonal functionalization [2]. The reactivity of the polymer structures was shown by covalent linkage of two different, chemically modified fluorophores. MPP scaffolds with bio-adhesive sites can also be used for 3 dimensional immunoassays [3] and for physiological studies in microfluidic channels.

Using carboxy-acrylate polymer structures in combination with a biotin modified supported lipid bilayer enables orthogonal functionalization with two different fluorescent proteins. One sort of proteins is immobilized on polymer anchors via nickel-nitrioltriacetic acid / histidine interaction. The other one is freely moving within the lipid bilayer surrounding the structures which is enabled using biotin / streptavidin binding [4]. As mobility of proteins and lipids plays a major role in physiological processes, this platform is well suited for modelling of cell interactions with mobilized and immobilized proteins and studying cellular response.

[1] Buchegger, B.; Kreutzer, J.; Plochberger, B.; Wollhofen, R.; Sivun, D.; Jacak, J.; Schütz, G. J.; Schubert, U.; Klar, T. A. *ACS Nano* **2016**, 10 (2), 1954-1959.

[2] Wollhofen, R.; Buchegger, B.; Eder, C.; Jacak, J.; Kreutzer, J.; Klar, T. A., *Opt. Mater. Express* **2017**, 7 (7), 2538-2559

[3] Wollhofen, R.; Axmann, M.; Freudenthaler, P.; Gabriel, C.; Röhrh, C.; Stangl, H.; Klar, T. A.; Jacak, J. *ACS Appl. Mater. Inter.* **2018**, 10 (2), 1474-1479.

[4] Buchegger, B.; Kreutzer, J.; Mayr, S.; Wollhofen, R.; Plochberger, B.; Axmann, M.; Jacak, J.; Klar, T. A., *submitted*.

9:00 AM BM05.01.04

Microengineered Human Blood-Brain Barrier Model with 3D Glia Network for Neuroinflammation Modeling and Nanomedicine Testing [Song Ih Ahn](#), [Jiwon Yom](#), [Hyun-Ji Park](#) and [YongTae Kim](#); Georgia Institute of Technology, Atlanta, Georgia, United States.

The blood-brain barrier (BBB) is a unique barrier of the central nervous system (CNS) that has a highly selective barrier function that prevents most drugs from entering the brain, leading to a high failure rate in the development of therapeutics for the CNS diseases. Currently there is a large unmet need for the development of new therapeutics for the CNS diseases with an increasing death rate of patients with CNS diseases like Alzheimer's disease (AD). One innovative approach to address this challenge is to develop a microengineered model of the human BBB that can mimic the pathophysiological conditions of the human brain. Yet, there is no physiologically relevant *in vitro* human BBB models that can incorporate shear stress, direct cell interactions, and 3D glial physiology of the human brain. Here we present a novel microengineered human BBB model designed to create a 3D co-culture of human brain endothelial cells (HBMECs), human brain vascular pericytes (HBVPs), human astrocytes (HAs) with the physiological morphology and interaction.

Furthermore, we construct a neuroinflammation model with 3D incorporation of human microglia (HM) to understand the role of microglia-mediated neuroinflammation in AD pathogenesis.

Our microfluidic BBB model consists of two layers separated by a porous membrane to mimic the luminal and abluminal regions of the BBB. After growing HBVPs on the abluminal side of the porous membrane, HAs were cultured in the same channel. As HAs cultured in 3D Matrigel showed more physiologically relevant morphologies with lower expression of reactive markers compared to that in 2D, the abluminal layer of our model was filled with HAs that are embedded in 3D Matrigel. This Matrigel was confined by surface tension from the two side channels that are designed for culturing HMs. HBMECs were cultured on the luminal side of the porous membrane and exposed to physiological shear stress that mimics blood flow in the brain microvasculature. As a result, our microengineered human BBB model showed a physiological network of the BBB cells with a polarized expression of aquaporin-4 to the luminal channel in astrocytic end-feet, highly specialized phenotypes of the brain endothelial cells with increased expressions of junctional proteins and solute-carrier genes, and a significantly decreased permeability of the endothelial monolayer, as compared to the monoculture of endothelial cells. Neuroinflammation model was constructed by adding HMs that were exposed to IFN- γ into the side channels of the stabilized human BBB model. HMs cultured in the side channels migrated into the Matrigel and showed a dynamic interaction with HAs, resulting in neurotoxic reactivities of HAs. Our microengineered BBB model can be utilized as a tool for the study of the pathological mechanisms of neuroinflammation and exploration of future therapeutic or preventive strategies for AD.

9:15 AM BM05.01.05

Surface-Attached Orthogonal Gradient Hydrogels Pandiyarajan Chinnayan Kannan and Jan Genzer; Chemical and Biomolecular Engineering, North Carolina State University, Raleigh, North Carolina, United States.

Gradient materials play a vital role in the creation of artificial implants due to their tendency to reduce stress concentration when two or more structures with different mechanical properties are joined together, *e.g.*, tendon, a fibrous protein that connects the soft and hard muscle tissues in our body. We demonstrate a versatile synthetic platform to mimic such gradient structures on flat supports using a random copolymer containing 90% of N-isopropyl acrylamide (NIPAAm), 5% photo-active methacryloyloxybenzophenone (MABP) and 5% thermally-active styrenesulfonfylazide (SSAz) crosslinkers. The presence of MABP and SSAz allows complete control over the gel density and stiffness in orthogonal directions by spatially and orthogonally controlling UV dosage and temperature. We examine the swelling ratio (α) of these gradient gels in water using spectroscopic ellipsometry; α depends on the extent of crosslinking that ranges from $\alpha = 1-1.2$ (highly crosslinked gels) to $\alpha = 4-5$ (loosely crosslinked gels). We corroborate the gel density with swelling and find that densely crosslinked gels promote protein adsorption (or cell adhesion) while the loosely-bound gels repel proteins and cells. We attribute the latter phenomenon to entropic shielding and size exclusion factors.

9:30 AM BREAK

10:00 AM BM05.01.06

3D Cultures From Rat and Human iPSC Derived Neurons Exhibit Epileptic Seizure-Like Activity Md Fayad Hasan¹ and Yevgeny Berdichevsky^{1,2}; ¹Department of Electrical and Computer Engineering, Lehigh University, Bethlehem, Pennsylvania, United States; ²Department of Bioengineering, Lehigh University, Bethlehem, Pennsylvania, United States.

Introduction: Most of the current epilepsy models use 2D neuronal cultures which cannot correctly mimic the cytoarchitecture of brain. State of the art 3D neuronal cultures use scaffolds which introduce foreign material and are often characterized by a lower cell density than the brain. Here, we present a simple yet novel and high-yield method to create polydimethylsiloxane (PDMS) confined scaffold-free 3D neuronal cultures from dissociated rat cortex and hPSC derived neurons that show spontaneous epileptic seizure-like activity without any convulsant agent. This method can potentially provide a new and better way for high-throughput anti-epileptic drug (AED) screening. A patient-specific drug development system also becomes feasible with the integration of hPSC with this technique.

Materials and Methods: We used PDMS to create 100 μm high micro-wells of different diameters (500-1500 μm). Dense solution of cells from neonatal rat cortex or hPSC derived neurons was put into these PDMS micro-wells. Diluted solution of cells was also seeded outside the PDMS to create 2D cultures. Ca^{2+} indicator (R-GECO1) was applied to these cultures. Optical recordings were performed on both 2D and 3D cultures from day in vitro (DIV) 08 to DIV 21 to observe the spontaneous activity. Multi-electrode array was used to measure the extracellular field potential. Cultures were fixed and stained with antibody to NeuN at DIV21 for confocal imaging. tetrodotoxin (TTX), kynurenic acid (KYNA) and different concentrations of AEDs, phenytoin, carbamazepine, levetiracetam and topiramate were applied to 3D cultures created with rat and hPSC derived neurons and the activity modulations were observed.

Results and Discussion: Optical and electrical recordings showed synchronous activity (bursts) across the whole culture in both 2D and 3D cultures. 3D cultures showed significantly different burst duration from 2D cultures. Burst duration increased significantly with increasing micro-well diameter for 3D cultures. Application of TTX and KYNA abolished all burst activities, indicating the key-role of neuronal firing and glutamatergic network behind this seizure-like activity. Application of different concentration of carbamazepine and phenytoin showed sigmoidal modulation of total activity time in 3D cultures. 3D cultures from hPSC derived neurons showed similar seizure-like activity and pharmacological response.

Conclusion: The data presented here proves the presence of epileptic seizure-like activity in the developed 3D cultures from neonatal rat and hPSC derived neurons. It further shows significant differences of activity patterns between 2D and 3D cultures. Pharmacological experiments on these cultures showed that they can be reliably used as a powerful tool for high-throughput drug screening for AED development.

Acknowledgments: This work was supported in part by NIH/NINDS R33 NS088358.

10:15 AM BM05.01.07

Biofabrication via Cytoprotective Polyphenol-Alginate Compartmentalization of Mammalian Cells in Photocrosslinkable Hydrogels Matthew Pan, Shengyang Chen, Tae-Sik Jang and Juha Song; Nanyang Technological University, Singapore, Singapore.

Biofabrication technologies have endowed us with the capability to fabricate complex biological constructs at exceptional resolution and accuracy. Photocrosslinking is commonly coupled with biofabrication to produce stable cell-laden hydrogels due to precise control in the polymerization process, short crosslinking times, and minimal heat production. However, there are three major drawbacks: 1) deleterious effects of UV irradiation such as DNA damage or the cancerization of cells, 2) radicals generated during irradiation which react with cells either via direct contact or the formation of reactive oxygen species, and 3) cytotoxicity from unreacted double bonds of hydrogels functionalized with photoreactive groups such as acrylates and methacrylates. Herein, we implemented a cell protection strategy against harmful external stressors present during biofabrication, which involves the encapsulation of mammalian cells within cytoprotective polyphenol-alginate compartments before embedding them in photocurable bioinks. Polyphenolics (PP) are especially suitable for encapsulation of cells due to the mild coating conditions required. Cell-laden alginate particles are generated followed by PP loading performed at various concentrations. The actual PP loading was quantified via UV-Vis absorbance spectrometry. The cytocompatibility and UV shielding effect of PP-alginate particles were thoroughly investigated with quantitative cell proliferation and LIVE/DEAD cell assays. Through our study, we discovered that even under prolonged UV irradiation (2.5-10 mins @ 18-19 mW/cm²), the viability of mammalian cells was preserved with the

encapsulation of cells in PP-alginate particles. Lastly, in order to evaluate the applicability of our cytoprotective PP-alginate particles in biofabrication, we tested them with three photocrosslinkable hydrogels, Poly(ethylene glycol) diacrylate (PEGDA; 10, 15%), gelatin methacryloyl (GelMA; 20%) and glycidyl methacrylate hyaluronic acid (GMHA; 4%). Hydrogel structures in the form of a thin substrate and a 3D printed scaffold were prepared at a particle to gel mass ratio of 2:3 and 1:3, respectively. The results clearly indicate that PP-alginate encapsulated cells exhibited higher viability under more stressful biofabrication conditions (extrusion-based 3D printing) and in more cytotoxic hydrogels such as PEGDA with high density of photoreactive side groups. The PP-alginate cell compartment acts not only as UV shield but also as diffusion barrier against harmful small molecules (photoinitiators) and larger macromolecules (polymer chains) as well as mechanical barrier against any external shear stresses. We envision this to be a technological breakthrough in biofabrication, maximizing mechanical stability of cell-laden scaffolds whilst minimizing damage to cells for any bioprinting or bioassembly processes.

10:30 AM BM05.01.08

Fabrication and 3D Morphologic Evaluation of Multicellular Tumor Spheroids Cassandra Roberge, David Kingsley, Denzel Faulkner, C.J. Sloat, Xavier Intes and David T. Corr; Rensselaer Polytechnic Institute, Troy, New York, United States.

3D tissue-engineered *in vitro* models, particularly multicellular tumor spheroids (MCTSs), are being increasingly used to explore disease progression and novel therapeutic strategies, especially for oncological applications. Once grown to 0.03-0.5mm³ in volume, these avascular constructs begin mimicking several key aspects of *in vivo* tumors, such as 3D structure and pathophysiological gradients. However, a lack of standardization of MCTS fabrication has led to a large variety of “spheroid” or “organoid” models, *many of which are unable to achieve the necessary morphology (i.e., size, sphericity) for physiologically-representative behavior*. Herein, we investigate the potential of laser direct-write (LDW) bioprinting to generate MCTSs in microcapsules and compare these to the gold standard technique in the field: liquid overlay.

Liquid overlay samples were prepared from MDA-MB-231 triple-negative breast cancer cells utilizing non-adherent, U-shaped 96-well plates, seeded either with (+) or without (-) the addition of 5% Matrigel growth factor (solubilized basement membrane from mouse sarcoma). The resulting cellular aggregates were imaged through maturity over a 4-day growth period via Optical Coherence Tomography (OCT) to assess construct morphology. Microcapsule fabrication was initiated by LDW printing of 400µm-diameter alginate microbead arrays containing MDA-MB-231 cells. These beads were incubated (~7min) in a chitosan-polysaccharide bath to create an alginate-chitosan polyelectrolyte complex shell around each bead, and then bathed briefly in sodium citrate to sequester the calcium and liquefy the bead cores. Following fabrication, the capsules were imaged via OCT over a 14-day maturation period.

By day 4, OCT imaging of the liquid overlay samples revealed disk-like aggregates in the absence of Matrigel, with low sphericity (0.597±0.01) and large volumes (0.390±0.011mm³) (n=6), as quantified by Imaris image analysis software. However, in the presence of Matrigel, cells formed highly spherical aggregates (sphericity=0.902±0.01) with compacted volumes (0.235±0.027mm³). Day 14 microcapsule imaging revealed the formation of spheroids with comparable sphericity to the Matrigel+ samples (0.862±0.04) with volumes of 0.061±0.008mm³.

Utilizing OCT, we monitored the development of 3D tumor models, and quantitatively assessed their evolving structures. Our findings show that while samples fabricated via liquid overlay reach physiologically-relevant sizes, the addition of Matrigel is essential for producing accurate 3D morphologies. Additionally, MCTSs formed via LDW were able to mimic this spheroidal morphology without the addition of exogenous factors. These findings have direct implications on the utility of direct-written MCTSs as *in vitro* tumor models for cancer research.

10:45 AM BM05.01.09

Scaffold Fabrication with Controllable Internal Architecture Ozlem Yasar¹ and Ozgul Yasar-Inccoglu²; ¹City University of New York, Brooklyn, New York, United States; ²Mechanical Engineering, California State University, Chico, Chico, California, United States.

Regenerative medicine bridges the engineering and life sciences to do organ or tissue regeneration. In this field, role of biomaterials, cell-cell interaction, and cell-scaffold interaction play a vital role in tissue regeneration. Biomaterials can be either synthetic materials or natural materials and they are widely used to either substitute a living system or fabricate the scaffolds. Scaffolds can be designed in the computer environment and they can be fabricated in the laboratory environment. In this research, scaffolds were designed with Lindenmayer Systems (L-Systems) and they were fabricated with photolithography. L-systems are rewriting processes that are used to design the fractals. Firstly, a single strut was drawn with the L-Systems and it was printed out by a 3-D printer. Then a y-shape, a trunk with three branches and a trunk with four branches were designed by L-Systems and they were also printed out with a 3-D printer. In this process, dissolvable filaments were used to print out the 3-D designs. Next, each of them inserted into liquid form of poly(ethylene glycol) diacrylate (PEGDA) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) mixture and exposed to the UV light for about 4 minutes. Because of interaction between UV light and PEGDA-DMPA mixture, polymerization occurred and the 3-D printed parts were trapped within the solidified hydrogel. Then, fabricated scaffolds were placed into the limonene bath, which helped to dissolve the filament away. These results showcases that PEGDA based hydrogel scaffolds can be designed with L-Systems to control the internal architecture of scaffolds and they can be fabricated with photolithography.

11:00 AM BM05.01.10

A Fast and Simple Replication Technique for Biological and Artificial Surfaces with Superhydrophobicity Jing Xiang², Hong Wang^{1,2}, Xun Zhu^{1,2}, Rong Chen^{1,2}, Yudong Ding^{1,2} and Qiang Liao^{1,2}; ¹Key Laboratory of Low-Grade Energy Utilization Technologies and Systems, Chongqing University, Chongqing, China; ²Institute of Engineering Thermophysics, Chongqing University, Chongqing, China.

Advances in microfluidics technologies have stimulated the development of new materials and the design of surfaces which should require hydrophobic surfaces and interfaces with low adhesion. Biological surfaces are good and natural models for the development of functional surfaces, such as wettability, optical characteristics and water directional transmission. Therefore, learning the microstructure of biological prototype is meaningful for the design of surfaces. Here, a novel and fast molding method has been used to replicate the microstructures of different leaves, and their surfaces decorated with Nano particles or wires by hydrothermal method, and eventually obtained the superhydrophobic property by silane treatment. Molding is a fast, simple and low-cost replication technique for biomimetic surfaces compared with other methods such as etching, lithography, electrochemical deposition and micromachining. The surface preparation process is as follows. At first, a negative is generated by molding. Then, we get the positive by filling the negative with liquid epoxy resin. In this way, we easily replicate the microstructure of lotus leaf, rice leaf and Salvinia Natans on the resin substrate. The method of molding easily gets the microstructure of various biologic surfaces, but the replicated surfaces just reach the hydrophobic degree after molding. As we know, there are many superhydrophobic plants with the hierarchical structure which combined with Micro and Nano Structures. Inspired by this, the ZnO hydrothermal method was used to build the nanostructure on the microstructure of molding, which was easy to control the length and diameter of nanohair. Specially, we focused on the most typical superhydrophobic plant —lotus leaf. Changing the concentration of ZnO growth liquid to control the nanostructure, the replica with 0.025M ZnO growth liquid (static contact angle 151°, sliding angle 6.5°) had a very close wettability with the original dry lotus leaf (static contact angle 152°, sliding contact 8.5°). Furthermore, we found the nanostructure is a key factor to achieve superhydrophobicity. The rolling contact angle increases with the increase of the length and diameter of nanostructure, which increases the solid-liquid contact area and reduces the air gap caused by the micro and nanostructure.

11:15 AM BM05.01.11

Cytocompatibility, Mechanical and Antibacterial Properties of the Eutectoid Ti-Ag Alloy Embedded with Hydroxapatite Nanoparticles [Lei Zhang](#)¹, Yuqin Zhang² and Yongmin Liu¹; ¹Northeastern University, Boston, Massachusetts, United States; ²Kunming University of Science and Technology, Kunming, China.

Extensive studies have indicated that integrating Ti metal of good mechanical properties with hydroxapatite (HA) ceramic of outstanding bioactivity and cytocompatibility can produce a suitable composite for biomedical implants. However, the addition of HA ceramic would deteriorate the mechanical durability and corrosion resistance of Ti alloy. In the present work, Ti-15.63 wt. % Ag alloy embedded with HA nanoparticles was synthesized by a combined route of spark plasma sintering (SPS) and mechanical alloying (MA). CaTiO_3 , $\text{Ca}_3(\text{PO}_4)_2$ and Ti_xP_y generated during a eutectoid transformation of $\beta\text{-Ti} \rightarrow \alpha\text{-Ti} + \text{Ti}_2\text{Ag}$. The dislocation movement of these ceramic phases regarding Ti_2Ag as a carrier boosts the mechanical durability of the composites. The *in vitro* test demonstrated that the Ti-15.63Ag-HA composites exhibit favorable mechanical durability, together with superior antibacterial properties (*S. aureus*) and cytocompatibility (MC3T3-E1). This work provides a strategy to design multifunctional Ti composites with enhanced mechanical properties and bioactivity and, specifically, the Ti-Ag-HA composite is expected to be a promising bone-implant biomaterial.

11:30 AM BM05.01.12

Assembly Controlled by Shape [Milana Lisunova](#)^{1,2}; ¹Ralph E. Martin Department of Chemical Engineering, 3202 Bell Engineering Center, UARK, Fayetteville, Arkansas, United States; ²School of Materials Science and Engineering, Georgia Institute of Technology, GATECH, Atlanta, Georgia, United States.

The shape factor is a critical parameter which impacts the assembly of the natural objects as well as artificial. Spontaneous assembly of micro- and nano-sized colloidal particles is a critically important process that plays a central role in the construction of biological structures and synthetic materials such as cells, viruses, bones, and nanocomposites.

One of the examples is ordered arrays of the spirulina cells which possess the disk-like shape of cells and tend to assemble to linear chains with wall-to-wall interactions of the cells. The same is synthesized cubic-like silver nanoparticles which primarily interact wall-to-wall and assemble to highly compacted cubic-like agglomerates. The detailed investigation of the cubic-like microcapsules versus spherical with the same nature of the surface and surface charges in the same aqueous buffer solution shows the predominant impact of shape on the assembly. Specifically, the spherical primarily assemble to chain-like structures while cubic forms the highly compacted "boxed" clusters. The chain spherical microcapsules are mobile and capable of reconfiguration due to the lower hydrophobic energy of attraction in contrast to compact, stable aggregates of cubic microcapsules. The dramatic differences in the assembly of microcapsules with similar nature but different shapes point to the aggregation behavior in such dispersions might be dominated by shape geometry and alternation of facet-to-facet interactions.

Understanding the principles of assembly of complex colloidal particles is a point toward novel advanced materials at which binding of the constructed blocks is governed mainly by shape geometry and anisotropic interactions which can be useful for further application in biomedical diagnostic technologies, tissue growth, and energy conversion.

The spirulina research was performed under supervision of Dr. Tammy M. Lutz-Rechtin. The assembly of the microcapsules were done with undergraduate student Neal Holland and graduate student Andriy Dorokhin. I am very much appreciate to Nano Bio Photonics group (nbphotonics.uark.edu) for the assistance with a Scanning Electron Microscopy. The work was supported by the U.S. Department of Energy, Office of Basic Energy Sciences, Division of Materials Sciences and Engineering, under Award # DE-FG02-09ER46604. The work also was supported by the University of Arkansas Foundation.

11:45 AM BM05.01.13

BioEmbroidery Technology as a Novel Approach for Additive Manufacturing of Structural Adapted Scaffolds for Tissue Engineering Applications Annette Breier, Judith Hahn, Cindy Elschner, Lars Bittrich and [Axel Spickenheuer](#); Leibniz-Institut für Polymerforschung Dresden e. V., Dresden, Germany.

Embroidery technology has been modified and established as Tailored Fiber Placement (TFP) in the early 1990th constituting a technical application to shape variable-axial composite parts with optimized strength and stiffness. Primarily destined for lightweight design, ten years later this technique was transferred to biomedical applications by processing biocompatible and surgical thread materials, now called *BioEmbroidery*. Unlike to the TFP-technology here the functional thread is processed directly by a multi-needle header generating porous structures suitable for cell substrates or tissue engineering scaffolds.

Due to the broad scope of textile parameters given by this technology the design of porous structures with space-resolved properties is possible. Crucial characteristics like pore size, available surface or mechanical properties can be tailored by processing parameters like stitch length, stitch angle or stitch alignment. The directed thread deposition enables the formation of meso-scaled structures with graduated properties.

Several applications for the tissue engineering of hard and soft tissues are possible and have been researched in various studies. Pore size and pore size distribution has been adapted in a scaffold for the tissue engineering of long bones. A load-bearing situation is given with the tensile stressed anterior cruciate ligament (ACL) requiring a triphasic scaffold structure mimicking the structural zones of bone, cartilaginous entheses and ligament (Hahner et al. 2015). Special features can be included during the *BioEmbroidery* process, for example a collagen barrier, separating the three structural zones during co-cultivation *in vitro* and thus avoiding cell migration of the different cell types (Breier et al. 2018). For hernia repair meshes need to feature high anisotropic structural properties matching the diversity of the mechanical behavior of the abdominal wall. While in the area of the hernia a high stiffness is required to reinforce the opening, a graduated transition of the stiffness slowly adapting to the properties of the surrounding tissue is seen as a remedy to avoid relapse. *BioEmbroidery* technology enables to manufacture hernia meshes with a high anisotropy complying these requirements. Prove was given by analyzing different stitching patterns with help of a digital image correlation system during biaxial testing.

1 References

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8:30 AM *BM05.03.01

Microengineered Physiological Biomimicry—Human Organ-on-Chips [Dan Huh](#); University of Pennsylvania, Philadelphia, Pennsylvania, United States.

Human organs are complex living systems in which specialized cells and tissues are assembled in various patterns to carry out integrated functions essential to the survival of the entire organism. A paucity of predictive models that recapitulate the complexity of human organs and physiological systems poses major technical challenges in virtually all areas of life science and technology. This talk will present interdisciplinary research efforts to develop microengineered biomimetic models that reconstitute complex structure, dynamic microenvironment, and physiological function of living human organs. Specifically, I will talk about i) bioinspired microsystems that mimic the structural and functional complexity of the living human lung in health and disease, ii) an organ-on-chip microdevice that emulates the ocular surface of the human eye, and iii) microengineered physiological models of human reproductive organs.

9:00 AM *BM05.03.02

Microfluidic Manipulation Based on Photodeformable Liquid Crystal Polymers [Yanlei Yu](#)^{1,2}, Jiu-an Lv^{1,2} and Quan Liu^{1,2}; ¹Department of Materials Science, Fudan University, Shanghai, China; ²State Key Laboratory of Molecular Engineering of Polymers, Shanghai, China.

Using light to manipulate liquid is a new paradigm for the actuation of microfluidic systems with contactless, spatial, temporal and precise control. Optical forces,^[1-2] light modulation of electrical actuation^[3-5] or light-induced capillary forces^[6-8] are three advanced approaches to convert light energy to liquid motion. The last one has advantages over the first two in that it requires neither special optical set-ups nor complex microfabrication steps.

Constructing microfluidic systems by photoresponsive materials is an efficient way to achieve light-induced capillary forces.^[9] Photodeformable liquid crystal polymers (LCPs) are ordered polymers that show large and reversible deformation and allow temporal, localized, remote and isothermal triggering and actuation.^[10-11] Hence, LCPs are good candidates for microfluidic actuators through photodeformation.

In recent years, we have designed a new strategy to manipulate fluid slugs by photo-induced asymmetric deformation of tubular microactuators (TMAs), which induces capillary forces for liquid propulsion. Microactuators with various shapes (straight, 'Y'-shaped, serpentine and helical) are fabricated from a mechanically robust linear liquid crystal polymer. These microactuators are able to exert photocontrol of a wide diversity of liquids over a long distance with controllable velocity and direction, and hence to mix multiphase liquids, to combine liquids and even to make liquids run uphill.^[12]

Moreover, optofluidic chips were fabricated to integrate multifunctional liquid manipulation through this new strategy and realize micro-analysis and bio-reactions in them. The liquid transportation, combination, mixing, reaction and detection in the chip are all controlled by light, which successfully simplify the microfluidic system by avoiding the connection of external pumps. We anticipate that these optofluidic chips will achieve the portability and domestic use of microfluidics and open a new door to the microfluidic area.

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9:30 AM BM05.03.03

Recreating the Hematopoietic Microenvironment *In Vitro* Using Microfluidic-on-a-Chip Technology Enables the Study of Interactions of Normal and Malignant HSPC with Specific BM Niches [Julio Aleman](#)¹, Sunil K. George¹, Samuel Herberg¹, Christopher D. Porada^{1,2}, Aleksander Skardal^{1,2,3} and Graça Almeida-Porada^{1,2,3}; ¹Wake Forest Institute for Regenerative Medicine, Winston Salem, North Carolina, United States; ²Virginia Tech-Wake Forest School of Biomedical Engineering and Sciences, Winston Salem, North Carolina, United States; ³Comprehensive Cancer Center at Wake Forest Baptist Medical, Winston Salem, North Carolina, United States.

Under normal conditions, hematopoietic stem/progenitor cells (HSPC) reside within specific bone marrow (BM) niches. These are comprised of an array of different cell types located strategically to provide myriad chemical signals and physical interactions that maintain HSPC^[1,2]. In human myeloid malignancies, the BM niche is remodeled by malignant cells, which displace resident HSPC, and create self-reinforcing malignant niches that drive disease progression, chemo-resistance, and relapse^[3].

We engineered a microfluidic platform, inside of which four individual hyaluronic acid-based niche constructs were patterned *in situ*^[4]. The corresponding niches contained BM-derived mesenchymal cells (Stro-1+; MSC), arterial endothelium (CD146+NG2+; AEC), and sinusoidal endothelium (CD146+NG2-; SEC). A fraction of the Stro-1+ cells were induced to undergo osteogenic differentiation, to generate osteoblasts (OB) for the fourth niche. U937 (lymphoma), MOLM13 (leukemia), and normal CD34⁺ cells were fluorescently tagged and independently perfused into the system.

At 24h post-infusion, U937 cells already exhibited a marked predilection for AEC, and this persisted throughout the 5-day observation period, with roughly 4.5-times more U937 cells engrafting within the AEC niche than the SEC or MSC niches, and 3-times more U937 cells engrafting within the AEC niche than the OB niche. In contrast, MOLM13 cells exhibited a marked preference for the OB niche, and a moderate affinity for the AEC, SEC, and MSC niches. In contrast to malignant cells, normal CD34⁺ HSPC did not show a dominant engraftment within the niches, but exhibited moderate preferential engraftment within the OB niche.

In conclusion, our studies establish the feasibility of using microfluidic "on-a-chip" technology to recreate the various niches within the BM microenvironment, and provide proof that this novel system can be used to study the interactions of normal and malignant HSPC with distinct cells of the niche. We are currently using this system to delineate the signaling pathways responsible for the observed preferential HSPC/niche cell interactions, with the ultimate goal of using this knowledge to develop more effective treatments for hematological malignancies and to enhance engraftment following HSC transplant.

9:45 AM BM05.03.04

Microfluidic Fabrication of Dynamically Trigger-Responsive Microcapsules as Actively Manipulatable Microreactors [Joerg Werner](#), Saraf Nawar, Zhang Wu, Brendan Deveney and David Weitz; Harvard University, Cambridge, Massachusetts, United States.

Exploring and analyzing processes in small volumes such as droplets enables the screening of large parameter spaces with only small amount of materials, but active and selective control over the supply and removal of molecular matter in these systems is a missing feature. In droplet microreactors, critical parameters such as reagents and their concentrations can be screened over a wide range for their chemical and biological activities. In biological systems in particular, the confinement to aqueous microdroplets allows for the analysis of cellular behavior on the single-cell level. In aqueous emulsion drop systems, however, nutrients and reagents have to be included during the drop formation or added via coalescence events. Furthermore, the harvesting of products for analysis and further processing without the destruction of the drop is often unattainable. The active manipulation over molecular access to such droplets without changes to the microreactors space itself would enable increased control on the picoliter scale and single-cell level. A trigger-responsive and permselective membrane around the water drop that acts as a gate-keeper allows to turn diffusion to and from the microreactor on and off controllably, to supply new reagents and nutrients or harvest products when needed, while keeping the active species trapped within the droplet. Here we describe a number of polymer chemistries that allow for the synthesis of functional water-cored microcapsules with tunable properties that are reversibly-responsive to various triggers. We employ microfluidic fabrication of double emulsion drops to synthesize trigger-responsive hydrogel membranes directly around water drops. These dynamic capsules can be repeatedly cycled between their permeable and impermeable state, enabling active control and manipulation over the accessibility of the capsule's aqueous interior with molecular selectivity.

10:00 AM BREAK

10:30 AM BM05.03.05

Perfusable Microvascular Networks On-Chip Enable Direct Measurement of Physiologically-Relevant Transendothelial Molecular Transport Giovanni Offeddu¹, Luca Possenti², Joshua Loessberg-Zahl¹, Maria Laura Costantino², Dean Hickman³, Charles Knutson³ and Roger Kamm¹; ¹Massachusetts Institute of Technology, Cambridge, Massachusetts, United States; ²Politecnico di Milano, Milan, Italy; ³Amgen, Cambridge, Massachusetts, United States.

The endothelium presents a critical barrier to molecular transport from blood to the interstitial space, hindering access of therapeutic proteins to their intended cellular targets. Understanding the physicochemical properties of protein therapeutics that affect transendothelial transport may aid development of therapeutic molecules with improved efficacy. Current *in vitro* methods that measure the distribution of these molecules are not representative of the complex human endothelium microenvironment and often yield results that are inconsistent with *in vivo* observations. Our microfluidic platform addresses this problem, by utilizing a three-dimensional microvascular network with significant morphological similarities to *in vivo* capillaries that enables spatiotemporal control over solute measurements within a microfluidic device. These microvascular networks are self-assembled from human umbilical cord endothelial cells (HUVECs) and human lung fibroblasts within seven days, and are fully perfusable over a range of physiological fluid pressures. Molecular transport measurements can be made as a function of intravascular pressure for a variety of macromolecules. Quantification is achieved with fluorescently-labeled solutes using time-lapsed confocal microscopy. Furthermore, because the pressure difference between lumen and interstitium produces transendothelial flow, interstitial fluid is expelled from the device and can be collected for direct sampling. Good agreement is observed between transport measurements made within the device and with the direct sampling method. We find that the endothelial resistance to the passage of both macromolecules and fluid are within the ranges observed *in vivo*. The mode of transport can be discerned between active and passive by considering the dependence of endothelial permeability on pressure. The approach we present allows for rapid measurement of physiologically-relevant transendothelial transport of labelled and unlabelled molecules. Therefore, this model system appears suitable to investigate the impact of physicochemical properties of therapeutic proteins on their relative biodistribution profiles.

10:45 AM *BM05.03.06

An Additive Manufacturing-Based Microfluidic System for Evaluation of Cancer Immunotherapies Ashley L. Beckwith^{1,2}, Luis F. Velasquez-Garcia² and Jeffrey T. Borenstein¹; ¹Biological Microsystems Group, Draper, Cambridge, Massachusetts, United States; ²Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States.

Microfluidic models of the tumor microenvironment typically comprise cultured cells or spheroids embedded in matrix materials, and have shown wide utility in the study of key phenomena involved in cancer progression, including angiogenesis, metastasis and intravasation. However, the recent emergence of immune checkpoint inhibitor (ICI) therapies highlight the need for model systems that can incorporate the dynamics of immune cell interactions with tumors, imposing additional design requirements for microfluidic systems as well as the need for higher throughput systems. These requirements include the incorporation of biopsied tumor fragments rather than engineered spheroids to better recapitulate the influence of matrix and stroma, extended operation while maintaining tumor viability in perfused media, and the ability to investigate tumor killing mediated by drugs either introduced directly into the system following treatment of extrinsic immune cell populations in a separable and quantifiable manner.

Here we report on the demonstration of a customized microenvironment for testing cancer immunotherapies, built using additive manufacturing techniques in a monolithic manner that enables an accelerated design-fabrication-testing development cycle. The central element of the model is a tumor trapping scheme that captures a biopsied fragment at the junction of a network of flow streams, permitting controlled introduction and flow rate of media containing drug compounds and potentially circulating lymphocytes to study specific mechanisms of tumor killing. The microfluidic device, which contains a tumor trap, loading channels and circulating media and tumor-infiltrating lymphocyte (TIL) channels as well as a bubble trap, is constructed using a monolithic three-dimensional printing process with spatial resolution on the order of 25 microns. Materials and processes for generation of these devices have been selected on the basis of cytotoxicity and optical transparency considerations, and experiments run for several days confirm viability of tumor fragments across the duration of studies. Initial results presented here demonstrate the effect of ICI on human non-small-cell lung cancers, presumably mediated by the action of the ICI treatment on resident TIL populations present in the tumors. These results point the way toward mechanistic studies of immunotherapies, either singly or in combination with small molecules or other ICI antibodies, that extend far beyond current capabilities offered by existing animal or tumor microenvironment models.

11:15 AM BM05.03.07

Fibrotic Microtissue Array to Predict Anti-Fibrosis Drug Efficacy Mohammadnabi Asmani and Ruogang Zhao; University at Buffalo, State University of New York, Buffalo, New York, United States.

Introduction: Pulmonary fibrosis, characterized by the progressive stiffening of lung's soft tissue, leads to organ failure and currently has no cure. Anti-fibrosis drug development is significantly limited by the long duration and high cost of clinical trials. Pre-clinical models that can recapitulate sophisticated biomechanical environment of lung tissue and provide early efficacy of the drugs are highly desired. Here, we create membranous human lung microtissues to model key biomechanical events occurred during lung fibrogenesis including progressive stiffening and contraction of alveolar tissue, decline in alveolar tissue compliance and traction force-induced bronchial dilation [1]. We then provide proof of principle for using this fibrotic tissue array for multi-parameter, phenotypic analysis of the therapeutic efficacy of two anti-fibrosis drugs recently approved by the FDA.

Method: UV photolithography of SU-8 photoresist and soft lithography techniques were used to fabricate arrays of PDMS micro-wells that contain square

configuration of micropillars. Primary human lung fibroblasts-mediated collagen matrix compaction was constrained by micropillar boundary conditions, leading to the formation of membranous microtissues with high span length to thickness ratios (S/t ratio) [1]. Microtissue array was bonded on a silicone sheet that was mounted on top of a stretching device. The effects of anti-fibrosis drugs, Nintedanib (Nint.) and Pirfenidone (Pirf.), on tissue mechanical properties and fibrosis biomarker expression were studied under static and dynamic culture conditions.

Results: We fabricated lung microtissue arrays in 12-well plate to enable parallel testing of multiple drug conditions. Cell-mediated matrix compaction leads to the formation of morphologically-controlled microtissues with high S/t ratio of 15 to 30, mimicking the membranous morphology of the thin lung alveoli sac walls. We showed that continuous TGF- β 1 treatment for 6 days caused significant increases in cellular α -SMA and pro-collagen expression, tissue stiffness and tissue contractile force as compared to untreated condition respectively, indicating the successful induction of fibrosis in the human lung microtissues. High concentration Pirf. at 5.3 mM completely inhibited α -SMA and procollagen expression. Microtissues treated with low concentration Pirf. and Nint. only partially attenuated TGF- β 1 induced increases in tissue mechanical properties, but high concentration Pirf. at 5.3 mM completely inhibited these increases. Under cyclic stretching, TGF- β 1 induced increase in tissue mechanical properties were inhibited by low concentration drugs. Together, these results demonstrate physiologically-relevant modeling capacity of the current system, which may become a powerful tool for the study of the action mechanism of drugs and the development of new anti-fibrosis drugs.

Reference: 1. Asmani M.& Zhao R. et al. 2018 Nature Communications. **9:** 2066 (2018)

11:30 AM BM05.03.08

Replicating Heterochronic Parabiosis on a Chip for Muscle Aging Study Yunki Lee, Song Ih Ahn, Jeongmoon Choi, Jiwon Yom, Eun Jung Shin, Young C. Jang and YongTae Kim; Georgia Institute of Technology, Atlanta, Georgia, United States.

Skeletal muscle has ability to repair due to the role of muscle satellite cells (MuSCs) in the regeneration but this capacity declines with aging. Recent *in vivo* studies using heterochronic parabiosis, in which two animals are surgically attached to share blood circulation, demonstrated that systemic factors in the blood of young animals can rejuvenate regenerative capacity of aged muscle. The exact mechanisms by which circulating youthful factors mediate the rejuvenating abilities of muscle stem cells, however, have yet to be elucidated. Due to the complexity of *in vivo* parabiosis and the dynamic nature of blood-borne factors, reliable identification of these humoral factors remains a major hurdle. To address this challenge, we leverage microengineering technologies to build 3D co-culture system of cells and tissues exposed to controlled biochemical cues with pathophysiological relevance. We first present a microvascularized MuSC niche on a chip (VMoC) designed to harness key characteristics of the native muscle microenvironment where MuSCs are cultured on a myofiber-laden 3D hydrogel covered by a vascular endothelial cells (ECs). We then employ our VMoC devices integrated to mimic heterochronic parabiosis to identify potential rejuvenating factors that enhance myogenesis of MuSCs.

Our VMoC was engineered using a double-layered microfluidic device that has 1) a top channel for the luminal side over a porous membrane, and 2) a bottom channel with a series of micropillars designed to confine the hydrogel. The primary MuSCs harvested from hind limb muscles of GFP-mice established multi-nucleated myotubes on the myofiber surface in the bottom channel, while immortalized mouse aortic ECs created a monolayer in the top channel. We first found that the MuSCs co-cultured with ECs significantly enhanced myogenic proliferation and differentiation as compared to the monoculture, while exhibiting similar differentiation to VEGF treatment to the monoculture. This result demonstrated that a biological paracrine effect of vascular ECs can be investigated in our chip 3D co-culture platform. We then found, more interestingly, that the administration of serum respectively isolated from young, old, and *Sod1*^{-/-} (oxidative stress-accelerated model) mice showed distinct myogenic activities of MuSCs; those treated with old and *Sod1*^{-/-} serum showed significantly lower myogenic differentiation. This result confirmed the ability of our VMoC platform to study systemic circulating factors in blood serum, and to test the rejuvenating effects in our integrated chip-to-chip platform that can replicate heterochronic parabiosis. We are currently using this technology to study heterochronic parabiosis between young- and old-VMoCs. With a precise control of systemic flow, our platform would address the critical barriers of *in vivo* parabiosis study, and serve as an experimental model to investigate the parabiosis mechanism in blood circulation in terms of muscle aging study.

11:45 AM BM05.03.09

Development of a 3D Microenvironment Model for Human Bone Metastases Antone Nour, Elie Akoury, Pouyan Ahangar, Michael Weber and Derek Rosenzweig; McGill University, Montreal, Quebec, Canada.

Bone is a dynamic tissue that is constantly broken down and repaired through a balance of osteoclast and osteoblast activity. However, when various cancers invade the bone, they can disrupt this balance leading to deleterious changes in bone structure and function. Radiotherapy, chemotherapy and surgical resection are the main clinical approaches to bone metastases. Studying cancer cells *in vitro* relies on 2D monolayer cultures which in no way represents the physiological tissue microenvironment *in vivo*. Therefore, preclinical and translational cancer research trends are moving toward organoid studies and 3D biomimetic models to provide more clinical relevance. Here, we set out to generate a bioink consisting of alginate, gelatin, and nano-crystal hydroxyapatite loaded with primary human osteoblasts and MSCs to produce a robust 3D bone-like microenvironment for studying human bone metastasis. A hydrogel (1% alginate; 7% gelatin) model for cancer cell-migration was modified to incorporate nanocrystal hydroxyapatite, primary human osteoblasts and primary human bone marrow derived stromal cells. Primary osteoblasts were isolated from vertebral bodies of organ donors and bone marrow MSCs were from Rooster Bio. The constructs were cultured for 28 days in either control medium (DMEM) or osteogenic medium (OM) with and without 0.5 mg/mL hydroxyapatite (HA). Live/Dead assays were performed to quantify viability and fixed frozen sections were stained with Alizarin red for calcified matrix deposition, and H&E to observe cells.

High osteoblast viability in all conditions was observed after 28 days of culture: 91.3 \pm 3.18 % for DMEM/HA⁺, 92.5 \pm 2.5 % for DMEM/HA⁻, 88.6 \pm 0.38 % for OM/HA⁺ and 85.9 \pm 6.2 % for OM/HA⁻. MSCs showed approximately 85.1, 69.4, 87.8 and 90% viability in the same four conditions. Alizarin red staining showed that cells grown in DMEM without HA had the least amount of bone mineralized matrix. The combination found to have the most amount of bone mineralized matrix was OM/HA⁺.

Our data indicate that combination of 0.5mg/mL nano-HA with OM produces a favorable bone-like microenvironment for primary human osteoblasts and MSCs. Our preliminary work with low-cost bioprinting indicates this bioink is extrudable and will be ideal for screening therapeutics against patient-derived tumor cells cultured within a bone-like microenvironment. Ongoing work is assessing migration of fluorescently labeled tumor cells within this construct in the presence or absence of various chemotherapeutics. Furthermore, ongoing immunostaining for collagen type I, osteopontin and sclerostin will elucidate presence of bone matrix and osteocytes within the model. This work will allow better understanding of interactions between normal osteoblasts, stromal cells osteocytes and patient derived bone metastases cells while also placing higher clinical relevance on therapeutics screening.

BM05.04.01

Effects of Mechanical Stresses on Granule Progenitor Cell Differentiation and Proliferation During Simulated Foliation Using a 4D Printed Cerebellar Cortex-on-a-Chip Timothy J. Esworthy, Shida Miao, Xuan Zhou and Lijie Grace Zhang; The George Washington University, Washington, District of Columbia, United States.

The cortex of the Cerebellum is involved in the regulation of a diverse array of cognitive and motor processes, which includes coordination of limb movements, speech vocalization, memory formation, and motor learning. Whereas the exact mechanism by which the Cerebellum regulates the variety of afferent signals it receives is the subject of current debate, it has been established that the manner by which its cortical circuitry is partitioned into discrete modular units, known as folia, plays an integral role. Therein, each individual folium of the Cerebellum is responsible for processing and actuating unique physiological functions. Seamless modulation of Cerebellum associated cognitive and motor processes has thereby been demonstrated to be contingent on the successful formation of hierarchical foliar structure. The complex process by which cortical folia develop (foliation) involves anisotropic patterning of Granule Progenitor cells (GPCs) around Radial Glial cell (RGC) associated anchorage centers. Moreover, previous studies have demonstrated that the rate of proliferation of GPCs around these RGC anchorage centers, and their capacity to differentiate into Granule cells (GrCs) as they migrate both radially and tangentially, is imperative for determining foliar shape and size. While much is known about the genetic pathways involved in the GPC to GrC differentiation process, the effects on GPC differentiation and proliferation conferred by the mechanical stresses they experience during foliation is largely unknown.

In our present study, we employ a novel 4D printing technique to fabricate a rationally designed chip model of the Cerebellar cortex, which we use to simulate the foliation process in order to query the effects that mechanical compression and stretching has on the proliferation rate and differentiation potential of seeded GPCs. In order to simulate the gyration and sulcation processes of foliation in a biologically relevant manner *in vitro*, we have fabricated our chip construct using a novel, carbon nanotube (CNT) functionalized shape-memory polymer. Our shape-memory polymer can be printed into a convoluted shape with anatomical geometries, flattened, seeded with GPCs, and will then return to its original folded shape in a physiologically relevant time-course when thermally triggered at 37°C. We are able to achieve favorable cellular adhesion to our printed chip construct by coating it with CNTs, which functionally operate as artificial extra-cellular matrix scaffolding for adherent cells. The progressive restoration of the original folded shape of the polymer faithfully simulates the foliation process and can exert compressive and stretching stresses on resident GPCs that are comparable to that of developing Cerebellar tissue.

BM05.04.02

Bioinspired Silicification on Close-Packed Silica Bead Arrays by Liquid Phase Deposition YunYeong Lee and Jin Seok Lee; Department of Chemistry, Sookmyung Women's University, Seoul, Korea (the Republic of).

Organisms can biosynthesize hierarchically patterned three-dimensional (3D) biominerals, called as biomineralization, such as calcium carbonate (mollusks shells), calcium phosphate (bone), and silica (diatom cell walls). The structural hierarchy in biominerals attributes strengths and stiffness, leading to protect themselves from natural environment. Especially, the process for production of silica into the living organism is known as biosilicification, which are often discovered in the diatom. Diatoms are complex and elaborated nano- and microstructured materials, whose architectures have numerous nanoscale pores with high porosity and high mechanical stability. Their extraordinary properties may have a potential for applications, such as sensors, molecular filters, and energy harvesting.

In this work, we explored the silicification on the arranged nanoscale-scaffold surface, such as the hexagonally close-packed silica bead arrays with porous structures, to mimic 3D hierarchical structures of diatoms by local liquid phase deposition. The energy and local concentration of silicic acid on the nanostructured surface are different; therefore, it is important to investigate the liquid phase deposition (LPD) on the nanostructure with diverse conditions to mimic and understand the mechanism of bioinspired morphogenesis. The different amount of water in LPD solution and reaction temperatures were used to investigate the effect of diverse environment because the biosilicification of diatoms occurs in the various surrounding environment such as concentration, temperature, and pressures. In addition, the silicification on the nanostructured surface deposited at the pinholes among the beads due to local high concentration, and this was monitored by Electrochemical Quartz Crystal Microbalance (EQCM).

BM05.04.03

Fabrication of Dome-Shaped Porous Alumina Microstructures and Their Applications for Drug Injector Yoobeen Lee and Jin Seok Lee; Sookmyung Women's University, Seoul, Korea (the Republic of).

Nanostructures are promising candidates to inject and control of active agents such as drugs or biomaterials into cells. In particular, porous alumina is widely used as a template for nano-sized materials due to its high surface area. Many previous studies have been investigated injection of drugs using porous aluminum, carbon nanotubes and nanocapsules as drug delivery systems. However, these drug delivery systems have some limitation to control the amount of injected drugs into cells.

In this work, we fabricated the dome-shaped porous alumina microstructures with hexagonal or cubic array, which are called simply 'microdomes', through the use of imprinting process on the initial surface over a large area with controllable diameter, thickness, and array. The different pitch of mold figure out the nanotopological effect on the size of microdomes, which are increase proportionally to distance between pushed parts. And, we investigated the formation process of dome-shaped porous alumina microstructures by gradual etching method, which is simple and fast to check the morphology of each stages. The different etching time was conducted to figure out the nanotopological effect on the morphology, which are range of 0 to 20 min. Furthermore, we investigated the microinjection efficiency for Hela cells by fluorescence colorization experiments confirmed drug delivery into the cells. These platforms could serve a model for the novel drug delivery system in many applications.

BM05.04.04

Optimization of Gold Nanostars Conjugated with Cell Penetrating Peptides for Intraoperative SERS Application Tatsiana Mironava¹ and Bruce E. Cohen²; ¹Stony Brook University, Stony Brook, New York, United States; ²Lawrence Berkeley National Laboratory, Berkeley, California, United States.

According to National Cancer Institute more than 12% of women in USA will develop invasive breast cancer during their lifetime. This project aims to develop imaging methodology based on SERS that combines sub-cellular resolution with ability to differentiate between normal and cancer cells. Amount of lipids in breast cancer cell is distinguishably different from the lipid content in normal and benign cells enabling cells distinction by means of Raman spectroscopy. Here we enhanced conventional Raman technique utilizing locally applied nanoparticles conjugated with cell penetrating peptides that ensure rapid nanoparticles penetration through the cell membrane. In this study normal and cancer breast cell lines - MCF-12 and MCF-7, respectively, were used. In addition, two types of nanoparticles - gold nanostars and nanospheres were conjugated to Tat-cell penetrating peptide for rapid intracellular delivery. Obtained results demonstrated sufficient differences in SERS spectra of cancer and normal cells providing the foundation for intraoperative cancer/normal tissue delineation by SERS imaging.

BM05.04.05

Engineered Phage-Based Immunostimulatory Materials for Virus Infectious Disease Hyo Jung Lee and Hyo-Eon Jin; College of Pharmacy, Ajou University, Suwon, Korea (the Republic of).

Enterovirus 71 (EV71) is a contagious virus can cause hand-foot-and-mouth disease, severe neurological complications and death most commonly in infants and children under 5 years of age. Prophylactic vaccine and therapeutic agent against EV71 infection are not clinically available yet. Inactivated EV71 is under developing as a vaccine still now, however, safer immunostimulatory materials need to be developed for infants and children. Here, we developed filamentous bacteriophage (phage) as an immunostimulatory material to deliver EV71 epitopes to elicit EV71-specific protective immune responses for preventing EV71 infection. The engineered phage-based immunostimulatory materials could be a promising vaccine because it is generally regarded as safe to human and cost-effective owing to its property that infects only bacteria. Engineered phages displayed the identified epitopes of EV71 in high valency on the major coat protein and ligand for inducing mucosal immune response on the minor coat protein of phages. Following two dosages of immunization in 6-week C57BL/6 mice, EV71-specific immune responses including both T cell independent and dependent antibodies were induced by phage-based immunostimulatory materials without adjuvant, and all data were compared to experiments using EV71 subunit proteins with adjuvant. Our immunostimulatory materials showed high immunogenicity as enough as preventing EV71 infection through EV71 challenge study. We expect that our phage-based immunostimulatory materials will be useful against the infection of various EV71 subgenotypes such as EV71 A, B1-5, C1-5 due to universal neutralizing epitopes on the major coat protein of the engineered phages.

BM05.04.06

Synthesis and Applications of Backbone Degradable Brush Polymers via ROMP Peyton Shieh and Jeremiah Johnson; Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts, United States.

Ring-opening metathesis polymerization (ROMP) has proven to be a powerful technique for the synthesis of highly functionalized polymer architectures due to its versatility and ease of use. A fundamental challenge, however, is the lack of degradability of the resulting polymer scaffolds. Here, I describe a general approach to impart degradability to polymers derived via ROMP. The resulting polymers show biodegradability tunable over orders of magnitude and the ability to degrade on demand in the presence of externally applied stimuli, enabling new applications in targeted drug delivery.

BM05.04.07

Mechanical Properties of Bio-Compatible Polymers Used for 3D Nanostructuring Boris Buchroithner^{1,2}, Yoo Jin Oh², Sandra Mayr¹, Dmitry Sivun², Peter Hinterdorfer², Thomas A. Klar² and Jaroslav Jacak¹; ¹School of Applied Health and Social Sciences, University of Applied Sciences Upper Austria, Linz, Austria; ²Department of Applied Physics, Johannes Kepler University, Linz, Austria.

Abstract

Multiphoton-polymerization (MPP), optionally combined with stimulated emission depletion (STED) lithography, allows two- and three-dimensional polymer structuring with sizes and resolution below the optical diffraction limit. Polymerization with photons in the visible range of the electromagnetic spectrum gives new opportunities in a large field of applications e.g. biotechnology and tissue engineering. Here, radical photoinitiator molecules (fluorophores) embedded in an acrylic negative tone photoresist are excited with a near infrared laser via two photon absorption; this allows writing of features as small as ~100 nm with a lateral resolution below 200nm.

For tissue engineering high standards regarding geometry and biocompatibility are required (e.g. mimicking the extracellular matrix or cartilage). Additionally, the materials have to be suitable for 3D MPP structuring, hence parameters like refractive index and cross-link rates of the monomers have to be considered. Typically for 3D lithography highly reactive, but toxic acrylate monomers are used. Alternatively, less-toxic methacrylates are less reactive and allow only a lower manufacturing velocity. Here we present a new type of biocompatible polymer, which combines the reactivity of acrylates, the biocompatibility of methacrylates and the stability of thiols. The resins are structured using MPP with a 515nm light source, a writing speeds up to several mm/s and sub-micrometer feature sizes. In order to characterize the mechanical properties of the manufactured scaffolds, atomic force microscopy was used. The Young's modulus of the polymers has been characterized and compared to different available resins. The biocompatibility of the polymer-structures has been probed via cell seeding.

BM05.04.08

Nano-Co with Hexagonal Unit Cell, Role in Lucerne (*Medicago sativa*) and Pea (*Pisum sativum*) Elizabeth Chavira¹, Adriana Nereida Avendaño Gavira¹, Guadalupe Zavala² and Adriana Tejada¹; ¹Universidad Nacional Autonoma de Mexico, Mexico, Mexico; ²Instituto de Biotecnología, Universidad Nacional Autónoma de México, Mexico, Mexico.

Report cobalt at nano-scale synthesis, with lucerne (*Medicago sativa*) and pea (*Pisum sativum*). For this nano-Co synthesis, Co_3O_4 (STREM CHEMICALS, 99.9985%) reagent was used. Analyzed by X-ray powder diffraction, (XRD) fine the Powder diffraction file, PDF 00-043-1003 and 3% of iron oxides (PDF's 00-008-0097 $Fe_2O_3 \cdot H_2O$, 00-002-0201 Fe_2O_3 orthorhombic, 00-016-0653 Fe_2O_3 monoclinic) impurities in the reagent. On one hand the lucerne (*Medicago sativa*) and pea (*Pisum sativum*) was growing in a clean environment, inside a wet sponge with micronutrients. The humidity in the laboratory goes during the growth from 30-70% (average value of 51%), controlling this by having the samples in a closed area. For seasons change and uncontrol about temperature, it was irregular throughout the growth, 17-24.6 C. Lucerne grown in 5 days and pea in 10 days. On the other hand, to characterize its growth, in a polluted- Co_3O_4 environment (0.05 g) the lucerne and pea seeds grew. Beside difference in growth, in comparison with the uncontaminated plants, the metal Co it is absorbing by root, stem and leaves. It is visualised that metal Co is distributing in small highly symmetric complex (similar) to virus like hexagonal crystal structure in infected cells.

BM05.04.09

Systematic Direction of Topological Defects in Cell Population by Computational Design of Geometrical Boundary Hiroki Miyazako, Tetsuhiko Teshima and Yuko Ueno; NTT Basic Research Laboratories, Atsugi, Japan.

In recent years, many researchers have been interested in the physical and biological roles of topological defects in biological tissues [1,2]. One of the main issues facing the study of these defects is the reproducibility with which they can be formed. Previous studies achieved the partial control of defect formation by culturing cells in a closed circular [1,2] or star-shaped [2] area. However, the position of the defects could not be precisely controlled, and no method has been established for designing the positions of defects in an arbitrarily shaped area. To solve this problem, this study proposes a systematic method for efficiently forming topological defects at specific points in a cell population by combining lithographic technology and computer-assisted design.

An overview of the proposed method is as follows. With our method, 2-methacryloyloxyethyl phosphorylcholine (MPC) polymers are patterned on a glass substrate, and closed cell adhesion areas are formed on the substrate. The patterned cells spontaneously form topological defects by proliferation and spontaneous alignment along the boundary between the MPC patterned and non-patterned areas. The positions of the defects in the cell adhesion area can be predicted by extending the results of [1]. First, two topological defects are placed in certain positions, and a Poisson equation is solved numerically to obtain the cell alignment. Then, the elastic energy of the cell population is calculated from the calculated cell alignment. By changing the position of the defects and iterating these three steps, the elastic energy of the cell population is minimized. The position of the defects is estimated as the acquired position with the minimum elastic energy.

The proposed method was confirmed experimentally as follows. We fabricated MPC polymer coated glass substrates that had cell adhesion areas with ellipsoidal shapes (major axis length: 300 ~ 800 μm , ratio of major/minor axes: 1 ~ 20). Then, NIH-3T3 or HFF cells were cultured on the substrate. When the ratio of the major and minor axes was about 2 ~ 3, two topological defects were reproducibly formed near the major axis as predicted by the above computational calculations. With the HFF cells, the defects vanished when the lengths of the major and minor axes were 600 μm and 400 μm , respectively. Considering that the HFF cell was larger than the NIH-3T3 cell, this result suggests that the sizes of the cells and defects are important when estimating the defect positions.

Our results showed that the direction of the topological defects could be achieved by computational calculations and that it is possible to design the optimal boundary for an efficient defect direction without using a trial-and-error approach.

References

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BM05.04.10

Engineering Perfusable Microscaffold for Meso-Physiological Systems Using Projection Micro Stereo-Lithography Pierre Sphabmixay, Linda G. Griffith and Nicholas Fang; Massachusetts Institute of Technology, Cambridge, Massachusetts, United States.

Current efforts in biomedical research are facing the necessity to improve *in vitro* systems towards more physiological and relevant models in order to recapitulate specific human *in vivo* mechanisms. The introduction of three-dimensional (3D) culture techniques have dramatically impacted our understanding of cellular biology and altered conclusions drawn from historically old two-dimensional *in vitro* models. The biggest challenge in the development of these 3D techniques remains the difficulty to sustain dense multi-cellular systems which requires to provide enough oxygen and nutrients deep within the tissue. In particular, the liver is one of the most difficult organs to culture in 3D *in vitro*, it constitutes only 2.5% of the total body mass but consumes 25% of the total cardiac output, making it unarguably the most oxygen and nutrient demanding organ of the human body, therefore requiring an extensively dense network of blood vessels in order to maintain its elevated metabolic activity. Furthermore, by being the central metabolizing organ in the human body, it is the organ most exposed to damage by chemicals and their metabolites entering the body. Pharmaceuticals pose a particular risk that can lead to drug-induced liver injury, whose mechanisms of actions are still poorly understood and are still the subject of controversy. For that reason, hepatotoxicity is a major cause for drug withdrawals from the market resulting in huge financial losses for the pharmaceutical industry. Therefore, tremendous efforts are being carried in order to improve current liver microphysiological systems (MPS) towards more predictive and physiologically relevant systems. Advances in micro/nano fabrication techniques offer promising solutions to tackle these challenges as they have enabled the development of devices and scaffolds capable of perfusing larger mass of cells, in combination with vascularization approaches in order to mimic the native microenvironment required for the cell function.

Here we have developed 3D perfusable scaffolds fabricated using Projection Micro-StereoLithography Apparatus (PuSLA) in order to provide improved 3D culturing techniques for liver MPS. Characterization of the fabrication technique allowed 3D printing of scaffolds with intricate architecture with resolution (3 microns) dramatically lower than the diffusion limit of oxygen (100 microns) therefore allowing efficient perfusion of dense tissue. Materials were engineered in order to feature favorable mechanical and biological properties for tissue formation and maintenance of mature phenotype. The designs of the scaffolds were optimized using a simulation approach by performing computational fluid dynamics in parallel with oxygen reaction simulation in order to predict viability of subsequent tissue *in vitro*. A commercially available bioreactor (Liverchip) was adapted in order to provide high flow rate and real time oxygen consumption monitoring.

BM05.04.11

Novel Microfluidic *In Vitro* Intestinal Model for Studying Drug Transport and Metabolism Haysam Ahmed¹, Yang Li², Igor Middel¹, Nick Langerak³, Jos Malda² and Rosalinde Masereeuw¹; ¹Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands; ²Orthopedics, Regenerative Medicine Utrecht, Utrecht, Netherlands; ³Physics, Institute for Theoretical Physics, Utrecht, Netherlands.

Caco-2 cells are widely used in pharmaceutical industry as a model to study intestinal absorption of drugs. Even though this 2D model provides enough insights into the intestinal absorption aspect, it lacks the metabolic functions that are exhibited *in vivo* (first-pass effect). In order to circumvent this shortcoming, a novel microfluidic device has been developed combining 3D printing, microfluidics and bio-functionalized hollow fiber membranes in one device.

3D printing is advantageous over the conventional soft lithography method for fabricating complicated structures, e.g., 3D flow chambers with hollow microchannels, microdevices with varying height in different locations. Moreover, it provides an alternative to polydimethylsiloxane (PDMS) that was shown to adsorb small molecules such as drugs hindering its use in a pharmaceutical setting. Here, we optimized the microfluidic design to allow for physiologically relevant shear stresses at low flow rates. The collagen-coated polyethersulfone hollow fiber membrane used in the developed device acts as a support for the cells and provides curvature to better mimic the *in vivo* microenvironment, thus providing both mechanical and dynamic signaling cues to Caco-2 cells to better differentiate into the various cell types observed in the human intestine.

The optimal shear stress rate was determined based on the cell differentiation (confirmed by immunofluorescent staining), villi formation, formation of a tight monolayer as a function of barrier function and more importantly enhanced metabolic function. In addition, it was shown for the first time that intestinal cells play a role in the generation of p-cresol metabolites, namely p-cresol sulfate and p-cresol glucuronide.

Taken together, this microfluidic gut device is a promising tool to study both the absorptive and metabolic functions of human intestine in pharmaceutical drug development compared to the currently used 2D models. Moreover, the modular design of the device allows for combining various organs to study not only the absorption but also metabolism (by connecting a liver device) and excretion (by connecting a kidney device).

BM05.04.12

A Convenient and Effective Antibiofilm Coating on Vascular Catheters Zheng Hou and M. B. Chan-Park; Nanyang Technological University, Singapore, Singapore.

Vascular catheters made from polyurethane (PU) are widely used in clinical settings and catheter-related infection are a serious clinical problem. It is mainly caused by the bacterial adhesion onto catheters' surface. Once bacteria attach onto a catheter surface, they likely develop into biofilm that are hard to eradicate. Hence, it is important to develop a catheter surface with antibiofilm ability. In this project, a convenient method of modifying PU catheter surface was developed and optimized. A zwitterionic monomer was coated onto a 30-cm long catheter surface via a polymerization technique to form a hydration layer that retards biofilm formation. To demonstrate the feasibility of the coating method for industrial application, a 30cm PU catheter was coated by the same method.

PU catheter was treated with ozone to introduce peroxide group on surface. Different concentration of [2-(Methacryloyloxy) ethyl] dimethyl-(3-sulfopropyl) ammonium hydroxide (SBMA) was dissolved in water and isopropanol (IPA) mixture. The solution was purged with Argon for 30mins. The catheters were then put into the solution; polymerization was initiated by addition of ammonium iron(ii) sulfate and carried for 24hrs. The antibiofilm efficacy of the coating was tested by incubation of the coated catheter in bacteria inoculum at 37°C for 24hrs and shows >99.0% prevention of surface biofilm for both Gram-Positive Methicillin-resistant Staphylococcus aureus (MRSA) and Gram-Negative Pseudomonas aeruginosa (PAO1). The antibiofilm efficacy of coated 30cm PU catheter was tested with an intraluminal microbial biofilm model and shows >99.5% inhibition of MRSA growth.

BM05.04.13

Effects of Bioink Rheological Properties on Stability of Extrusion Bioprinting Reza Avaz³ and Amir K. K. Miri^{1,2}; ¹Rowan University, Glassboro, New Jersey, United States; ²Bioengineering, University of California, Los Angeles, Los Angeles, California, United States; ³Institute for Computational Engineering and Sciences, University of Texas at Austin, Austin, Texas, United States.

3D Printing techniques have been flourished in the fabrication of advanced scaffolds for tissue engineering and regenerative medicine. For selected platforms, bioink formulation should be optimized for the desired application, in which it requires a deep understanding of bioprinting mechanism. The hydrogel-cell bioink is printed as a sol-state and then solidified following the deposition (or dispensing) process. This deposition process is occurred in extrusion-based bioprinting technique, which uses a cone-shape nozzle head to deposit the bioink. The deposition process ideally leaves spatially-controlled continuous strands of the bioink. However, mechanical issues can lead to instability of the deposited strands. The presence of mechanical instability can generate oscillatory forces and kinetics-related stress components that affect the behavior of cellular components within the hydrogel. This further hampers the printing resolution. A key factor in designing bioinks and selecting bioprinting parameters is to minimize instability of the bioink after leaving the nozzle. Although cell-laden bioinks often possess significant non-Newtonian properties, such as power-law and yield stress behaviors, the effect of such properties on the stability and spatial resolution of the fluid deposition has not been studied. In this work, assuming a slender flow model, we estimated the onset of instability as functions of the rheological properties of the fluid, such as rate-dependent viscosity and yield stress, as well as the geometry of the nozzle, such as size and bluntness. A moderate shear thinning behavior was found to stabilize the deposition process; in contrast, a high yield stress led to an unstable deposition of the bioink on a stationary substrate. The long-term goal of this work is to provide a simulation-assisted framework for high-fidelity 3D-printing of cell-laden bioinks.

BM05.04.14

Fabrication of Complex Vasculatures by 3D Printed Biomaterials Terry T. Ching^{1,2,3}, Yi-Chin Toh³ and Michinao Hashimoto^{1,2}; ¹Pillar of Engineering Product Development, Singapore University of Technology and Design, Singapore, Singapore; ²Digital Manufacturing and Design Centre, Singapore University of Technology and Design, Singapore, Singapore; ³Department of Biomedical Engineering, National University of Singapore, Singapore, Singapore.

3D printing has enabled the fabrication of microfluidic devices, but it remains challenging to recapitulate the full complexity of the architecture in vasculatures. Despite several approaches used to print vascular-inspired features (such as sacrificial molding and embedded 3D printing), the complex hierarchical branching networks as seen *in vivo* is yet difficult to achieve by 3D printing. Herein, we proposed a design approach that enables existing commercial 3D printer to fabricate complex vasculatures in biocompatible hydrogels. Instead of directly printing the entire network as a unibody, our approach involved the decomposition of the system into simple and printable elements. We demonstrated to use two materials with different Young's modulus to fabricate such 3D networks—exterior elements printed in rigid polymers and interior elements printed in elastomeric polymers—to obtain tightly sealed 3D microchannels. The rigid elements served as an exterior shell to secure the interior elements in place while the elastomeric nature of the interior elements made conformal contacts when compressed, confining fluid in its intended space to form complex networks of microchannels. We used polymer jet (PJ) and stereolithography (SL) printers to demonstrate fabrication of vascular-inspired networks such as rectilinear lattice and helical networks of microchannels. Hierarchical branching of 1, to 4, to 16 channels with diameter of 850, 600 and 250 µm were achieved with the spacing between channels below 300 µm within the oxygen diffusion limit of 200 µm. The same strategy was applied to fabricate vascular-inspired networks in a biocompatible composite material. The assembled 3D microchannels were readily disassembled for imaging of different segments of the microchannels. Overall, we developed a design approach to enable 3D printing of complex vasculature-inspired architecture of microchannels. This is a general approach that can be demonstrated by most commercial 3D printers. To our knowledge, this is the first demonstration to fabricate 3D microchannels at this complexity (i.e. hierarchical branching) and the size scale (spacing between channels are maintain below 300 µm). Our current work opens opportunities to fabricate microchannels in a wide array of biomaterials. Devices created in this approach shall serve as effective *in vitro* model for vascularized tissue engineering, bioinspired surrogates for drug development, and regenerative medicine.

BM05.04.15

Engineering a Synthetic Analogue to the Nucleus Pulposus for Spinal Disc Repair Therapies Juyi Li, Clement Marmorat, Yeshayahu Talmon, Raphael Davis and Miriam Rafailovich; Stony Brook University, Stony Brook, New York, United States.

The role of synovial fluids is to enable frictionless motion of joints and provide shock absorbance within the spinal cord for the central nervous system. Injury, disease, and even aging can degrade the structure and mechanical response of the fluid. Here we report on engineering a substitute for the nucleus pulposus, the viscous fluid within the spinal cord discs. Herniation of lumbar discs is a painful condition, which often requires surgical intervention, where the nucleus pulposus is removed and the disc space is fused. Recently hydrogels have been proposed as possible replacements. Yet, despite a great deal of effort, several major challenges must be overcome; The materials are tough and yet injectable and extremely flexible, biocompatible and yet non-adhesive and resistive to enzymatic degradation. Consequently a variety of chemically cross linked synthetic gels or viscous natural hydrogels have not been successful. Here we report on the use of Pluronic physical gels, which we have successfully bioprinted, injected, and shown to prevent scarring and degradation *in-vivo* in dog trials. The results were very surprising since, despite their tremendous mechanical flexibility, these tri-block copolymers are very sensitive to fluid volume changes. We demonstrate, using SEM microscopy on gel cryo-sections, together with *in-situ* x-ray analysis, that in addition to the standard parameters defining the equilibrium state, the stability of physical gels is dependent on the dynamical aspects of the fluid medium. Using a specially constructed flow chamber, we show that for a Pluronic F127 physical gel, the degradation process can be greatly reduced under high fluid flow rate tangential to the gel surface. Since the physical gel is formed by an ordered crystal of micelles, stabilized by entanglements within their coronas, a simple model is proposed where swelling can occur only when the flow rate is less than the reptation time. Otherwise, rather than dissociating into individual micelles, the micelle gel responds collectively to the surface shear forces as an elastic solid, which deforms in a direction perpendicular to the

flow in order to minimize stress. This aspect of the Pluronic triblock copolymer system greatly extends their application from an injectable drug delivery carrier to a structural component which is at once injectable, and yet able to sustain deformation and resist dissolution in physical fluids.

[1] Bhatnagar, Divya, Miriam Rafailovich, and Raphael Davis. "Methods Useful in Optimizing the Treatment of Neuropathies and Targeting Tissues with Cosmetic Botulinum Injections." U.S. Patent Application No. 13/463,766.

SESSION BM05.05: Biomaterials and Tissue Microenvironment
Session Chairs: Jianping Fu and Yu Shrike Zhang
Thursday Morning, November 29, 2018
Sheraton, 2nd Floor, Liberty C

8:00 AM BM05.05.01

Effect of Freeze-Thaw Cycle on the Energy Storage of PVA-Gelatin Theta-Cryogels Patrick Charron¹ and Rachael A. Oldinski^{1,2}; ¹Department of Mechanical Engineering, University of Vermont, Burlington, Vermont, United States; ²Department of Electrical and Biomedical Engineering, University of Vermont, Burlington, Vermont, United States.

Poly(vinyl alcohol) (PVA) is a synthetic, biocompatible polymer that has been widely studied for use in bioengineered scaffolds due to its highly attractive properties, such as high strength, creep resistance, and porous structure. These properties can be fine-tuned by controlling the physical, non-covalent crosslinks through various techniques. Typically, PVA hydrogels are relatively brittle, non-elastic materials. Blending in gelatin, a natural collagen derivative, and using poly(ethylene glycol) (PEG) as a porogen for theta-gel formation, forms a highly organized, cell-instructive hydrogel with increased stiffness. Theta-gels are formed from the solidification and phase separation of high molecular weight gelatin and PVA from low molecular PEG during a decrease in temperature. To increase the stiffness and energy storage of PVA-gelatin theta-gels, the materials were additionally processed using cryo-gel techniques, which involved freezing theta-gels, lyophilizing and re-hydrating. The result was a stronger, more elastic material. Compressive rheological data suggest significant changes in the elastic modulus of PVA-gelatin theta-cryogels with increasing freeze-thaw cycles. The crystallinity as measured by Fourier transform infrared spectroscopy increased with increasing freeze-thaw cycles. Scanning electron micrographs showed an increased pore size of the PVA-gelatin theta-cryogels with increasing pore size, as expected from reports in the literature. Interestingly, however, the more crystalline materials demonstrated an increase in energy dissipation, which may be reflective of a higher water content. It is hypothesized that a stiffer material with larger pores may contribute to increased fluid flow, creating a tough yet resilient material for soft tissue repair.

8:15 AM BM05.05.02

Scalable Production and Cryo-Storage of Organoids Using Core-Shell Decoupled Hydrogel Capsules Yen-Chun Lu; Cornell University, Ithaca, New York, United States.

Organoids, organ-mimicking multicellular structures derived from pluripotent stem cells or organ progenitors, have recently emerged as an important system for both studies of stem cell biology and development of potential therapeutics; however, a large-scale culture of organoids and cryopreservation for whole organoids, a prerequisite for their industrial and clinical applications, has remained a challenge. Current organoid culture systems relying on embedding the stem or progenitor cells in bulk extracellular matrix (ECM) hydrogels (e.g., Matrigel™) have limited surface area for mass transfer and are not suitable for large-scale productions. Here, we demonstrate a capsule-based, scalable organoid production and cryopreservation platform. The capsules have a core-shell structure where the core consists of Matrigel™ that supports the growth of organoids, and the alginate shell forms robust spherical capsules, enabling suspension culture in stirred bioreactors. Compared with conventional, bulk ECM hydrogels, the capsules, which could be produced continuously by a two-fluidic electrostatic co-spraying method, provide better mass transfer through both diffusion and convection. The core-shell structure of the capsules also leads to better cell recovery after cryopreservation of organoids probably through prevention of intracellular ice formation.

8:30 AM *BM05.05.03

Synthetic Human Embryo-Like Structures—A New Paradigm for Human Embryology Jianping Fu; Mechanical Engineering, University of Michigan, Ann Arbor, Ann Arbor, Michigan, United States.

Early human embryonic development remains mysterious due to drastic species divergences between humans and other mammalian models and limited accessibility to human embryo samples. Recent studies from my laboratory and others have shown that under suitable culture conditions, human pluripotent stem cells (hPSCs) can undergo intricate morphogenetic events and self-organize to form patterned human embryo-like structures *in vitro*. These synthetic human embryonic tissues hold great promises for advancing human embryology and reproductive medicine. In this talk, I will first discuss a micropatterned hPSC-based neuroectoderm patterning model, wherein pre-patterned geometrical confinement induces emergent patterning of neuroepithelial and neural plate border cells, mimicking neuroectoderm regionalization during early neurulation. In the second part of my talk, I will discuss a hPSC-based, synthetic model of early human post-implantation development that recapitulates key developmental landmarks successively, including pro-amniotic cavity formation, amnion-epiblast patterning, primordial germ cell specification, and development of the primitive streak with controlled anteroposterior polarity. Together, our studies have developed powerful synthetic embryological platforms and provided new understandings of previously inaccessible but critical embryogenic events in human development.

9:00 AM BM05.05.04

Formation of Planar Intestinal Crypt with Distinct Proliferative and Differentiated Regions Rachyun (. Kim¹, Yuli Wang², Shee-Hwan J. Hwang², Peter J. Atteyak¹, Nicole M. Smiddy², Christopher E. Sims¹ and Nancy L. Allbritton^{1,2}; ¹Joint Department of Biomedical Engineering, UNC at Chapel Hill and North Carolina State University, Chapel Hill, North Carolina, United States; ²Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States.

A simple *in vitro* intestinal model system that recapitulates key aspects of the intestine *in vivo* can enhance our understanding on the physiology of the intestine and the impacts of drugs or biochemical stimuli such as metabolites and signaling molecules. We developed a planar platform recapitulating the segregation of the three-dimensional intestinal epithelial cells *in vivo*. A thin layer of collagen was overlaid onto microhole array made of an impermeable photoresist film, creating two distinct regions with different porosity and stiffness. When mouse primary colon epithelial cells were grown on the platform, the cells formed a monolayer across the microhole array with segregated cell populations: proliferative cells over the microholes and non-proliferative cells distant from the microholes. Generation of growth factor gradients across the cells via the microholes resulted in *in vivo*-like cell behaviors where

proliferative cells over the microholes migrated outward, differentiated as they migrated and then eventually reaching the end of their lifespan in regions apart from the microhole sources of growth factors. Short chain fatty acids, bacterial metabolites that are present in the colonic lumen, significantly influenced the proliferation and differentiation of the primary mouse colon epithelial cells as has been demonstrated to occur *in vivo*. With simple fabrication, ease of use, and low maintenance, this platform enables observation and quantification of proliferative and differentiated cells simultaneously and the interplay between these two cell zones. Access to both the luminal and basal sides of the polarized tissue permits the screening of drugs, metabolites and food stuffs for their impact on intestinal cell epithelium. This platform will be a valuable tool for to understand intestinal physiology in health and disease.

9:15 AM BM05.05.05

Folding Artificial Mucosa with Cell-Laden Hydrogels Guided by Mechanics Models Ruiké Zhao^{1,2}, Hon Fai Chan¹, German A. Parada¹, Kam W. Leong³, Linda G. Griffith¹ and Xuanhe Zhao¹; ¹Massachusetts Institute of Technology, Cambridge, Massachusetts, United States; ²Mechanical and Aerospace Engineering, The Ohio State University, Columbus, Ohio, United States; ³Columbia University, New York, New York, United States.

The surfaces of many hollow or tubular tissues/organs in our respiratory, gastrointestinal, and urogenital tracts are covered by mucosa with folded patterns. The patterns are induced by mechanical instability of the mucosa under compression due to constrained growth. Recapitulating this folding process *in vitro* will facilitate the understanding and engineering of mucosa in various tissues/organs. However, scant attention has been paid to address the challenge of reproducing mucosal folding. Here we mimic the mucosal folding process using a cell-laden hydrogel film attached to a pre-stretched tough-hydrogel substrate. The cell-laden hydrogel constitutes of human epithelial cell lining on stromal component to recapitulate the physiological feature of mucosa. Relaxation of the pre-stretched tough-hydrogel substrate applies compressive strains on the cell-laden hydrogel film, which undergoes mechanical instability and evolves into morphological patterns. We predict the conditions for mucosal folding as well as the morphology of and strain in the folded artificial mucosa using a combination of theory and simulation. The work not only provides a simple method to fold artificial mucosa but also demonstrates a new paradigm in tissue engineering via harnessing mechanical instabilities guided by quantitative mechanics models.

9:30 AM BM05.05.06

Alginate-Based Electrodeposition for On-Demand Fabrication of Tubular Structures for Applications in Vascular Tissue Engineering David Kingsley, Jared Capuano, Rachel Antmann, Cassandra Roberge and David T. Corr; Rensselaer Polytechnic Institute, Troy, New York, United States.

One of the major challenges in tissue engineering is the fabrication of tubular cell-loaded structures (e.g., blood vessels). This is due, in part, to the difficulties in generating a self-supporting luminal structure with an appropriate spatial distribution of loaded cells. Alginate - a polysaccharide derived from brown algae that gels in the presence of divalent cations, such as Ca^{2+} - has gained great traction as an exciting candidate material for biofabrication, due to its tunable mechanical properties, ease of gelation, overall biointertness, and ability to be gently resolved through reverse crosslinking. Typically, alginate structures are created through homogenous internal crosslinking systems in which insoluble CaCO_3 particles are suspended in an alginate solution, and the calcium slowly dissociates from the carbonate upon introduction of a weak acid (e.g., GDL), to crosslink the alginate network. Recently, electrolysis has been shown as an alternative method to generate crosslinked alginate gels. In this method, a current is run through an electrolyte solution to produce products of hydrogen and carbon dioxide, with a reaction byproduct of protons generated at the anode surface. These protons can be exploited to produce free calcium from CaCO_3 and cause local crosslinking when performed in an alginate solution. Herein, we utilize electrolysis to produce a pH change at a cylindrical copper anode surface, resulting in the radial deposition of an alginate gel around the anode wire. Furthermore, we investigate how alginate deposition is effected by key variables in the fabrication process, including: applied voltage, CaCO_3 particle size, anode wire diameter, alginate concentration, calcium concentration, and overall electrolysis duration. Within these experiments, the rate of alginate deposition increased inversely proportionately with CaCO_3 particle size (and therefore available surface area), however this effect appeared to diminish at longer deposition times. Furthermore, we observed that greater diameter anode wires were able to produce thicker gels, likely due to the available surface area for proton generation. Similarly, alginate and calcium concentration also affected the thickness of deposited gels on anode surfaces, and the overall robustness of the gels (qualitatively speaking). Last, we apply this technique to generate alginate tubular structures entrapping multiple layers of discretized cells. By performing sequential electrodeposition using two different alginate solutions, suspending either GFP or RFP labeled cells, we observe via fluorescent microscopy radial compartmentalization, i.e., the encapsulation of each cell line at different layers in the luminal thickness. Overall, within this work we demonstrate a novel, on-demand technique to fabricate alginate-based tubular structures with encapsulated discretized cells, using the principles of electrodeposition.

9:45 AM BREAK

SESSION BM05.06: Sensors for Monitoring Tissue Models
Session Chairs: Jing Tang and Weijia Zhang
Thursday Morning, November 29, 2018
Sheraton, 2nd Floor, Liberty C

10:15 AM BM05.06.01

Nanowire Arrays Restore Vision in Blind Mice Jing Tang; Materials Science and Engineering, Stanford University, Stanford, California, United States.

The restoration of light response with complex spatiotemporal features in retinal degenerative diseases towards retinal prosthesis has proven to be a considerable challenge over the past decades. Herein, inspired by the structure and function of photoreceptors in retinas, we develop artificial photoreceptors based on gold nanoparticle-decorated titania nanowire arrays, for restoration of visual responses in the blind mice with degenerated photoreceptors. Moreover, neurons in the primary visual cortex respond to light after subretinal implant of nanowire arrays. Improvement in pupillary light reflex suggests the behavioral recovery of light sensitivity. Our study will shed light on the development of a new generation of optoelectronic toolkits for subretinal prosthetic devices.

10:30 AM BM05.06.02

A Novel Technique for *In Situ* Characterization of 3D Tissues Using MEMS Mohamed Elhebeary and Taher Saif; University of Illinois-Urbana Champaign, Urbana, Illinois, United States.

The development of multicellular tissues is highly dependent on the mechanical forces associated with cell-cell and cell-matrix interactions. Cellular forces are measured using Traction Force Microscopy (TFM) on 2D soft substrates. However, TFM cannot provide forces in 3D tissues. Also, the effect of cross talk between cells within the tissue microenvironment cannot be captured in 2D culture. Here, we propose a technology that introduces a new device and a new method that radically changes the way we form 3D biomimetic tissues, and study them *in situ*. The method exploits the advances in micro-fabrication and combines them with classical theories of capillarity to offer new functionalities, namely self-assembly and self-alignment of tissues on a sensor stage. Currently there is no technology available to measure tissue force (due to cells) and tissue stiffness simultaneously. The new device closes this gap for the first time. It not only provides a time lapse measure of both force and stiffness, it allows simultaneous inspection of the microstructure of the tissue *in situ*, thus linking tissue biophysics with pathophysiology. Such *in situ* quantitative inspection will offer new insights that cannot be achieved with existing methods.

A novel design of a silicon platform, that integrates a stretching and sample self-assembly mechanisms, is introduced. First, a mixture of collagen I solution and fibroblasts (3T3) is dispensed on the silicon platform at room temperature (500x500x200 μm^3). After curing, the chip is inundated in cell culture media within an incubation chamber. The small thickness of the chip (200 μm) makes it compatible with live cell microscopy and avoids any histological sectioning needed in the case of thick sample. The tissue forces are measured using an optical microscope by imaging the co-fabricated gauges on the chip and follow-up image analysis. An external 3D manipulator is used to stretch the tissue sample to measure its elastic modulus at different stages of tissue morphogenesis. Image analysis gives a displacement resolution of approximately 200 nm and a corresponding force resolution $<1 \mu\text{N}$. The proposed technology offers advantages over available techniques to study the biomimetic tissue due to the following reasons: no need to expose the sample to light which might affect its response, small size allows portability between different chambers during imaging and/or incubation, and ability to monitor the stiffness change along with microstructure development with time. Results from different cell lines showed the evolution of force with time after seeding cell/collagen mixture. Stiffness measurements of samples and effect of drugs on force relaxation are studied.

10:45 AM BM05.06.03

Improvement Performance of Ionic Liquid-Based Pressure Sensor for Integration into Body-on-a-Chip Yusuke Tsuji, Yoshikazu Hirai, Ken-ichiro Kamei, Toshiyuki Tsuchiya and Osamu Tabata; Kyoto University, Kyoto, Japan.

Body-on-a-Chip (BoC) platform holds a great potential for new pre-clinical tests in drug screening as *in vitro* human models by mimicking *in vivo* physiological and pathological conditions. Recently, the authors have reported a proof of BoC concept for recapitulation of the cardio-toxic side effects of an anti-cancer drug [1]; however, there is still a technological challenge to integrate a pressure sensor for monitoring or controlling pressure in BoC, leading to create cellular microenvironments close to *in vivo* physiological conditions in the BoC platform. Among existing polydimethylsiloxane (PDMS)-based pressure sensors, the sensor with ionic liquid (IL pressure sensor) [2] is promising due to allowing direct integration into a PDMS-based BoC platform by multilayer soft lithography. But previously reported sensors lack proper performance with respect to sensitivity and linearity. Here we propose a novel fabrication approach of an IL pressure sensor by using simulation-based three-dimensional (3D) lithography and show its improved sensor performance.

An IL pressure sensor is composed of a flow channel to circulate cell culture medium and an electro-fluidic (EF) channel filled with IL, and they are overlapped with separation by a PDMS membrane (tens of μm). The pressure in flow channel can be measured by monitoring electrical resistance change of an EF channel induced by membrane deformation by pressure. Since the sensor performance such as sensitivity and linearity depend on cross-sectional shape of the EF channel, we focused to tune a cross-sectional shape of mold for EF channel.

To improve the sensor performance, the electrical resistance change of EF channel by deformation of PDMS membrane were simulated with FEM analysis for four sensors with different cross-sectional geometries (rectangle: 400, 600 μm width x 25 μm height, triangle: 400 x 25 μm^2 , and semi-ellipse: 400 x 25 μm^2). The triangular channel showed 10-time higher sensitivity than the rectangular channel.

Then, designed sensors were fabricated by digital micromirror device-based grayscale lithography [3] with a numerical process optimization, and resistance changes were measured by an impedance analyzer. The results on static pressure with the range of 0 to 12 kPa exhibited good agreement with the numerical simulation results. Moreover, to validate the performance to measure heart beating, the periodic pressures with a triangular wave were applied to the sensor. As the results, the sensor with triangular channel was able to follow at least pressure change at 1 Hz. We believe that our proposed approach and developed sensor will allow measuring pressures at the physiological levels.

[1] K. Kamei et al., RSC Adv., 7 (2017), pp.36777–36786.

[2] C.-Y. Wu et al., Lab Chip, 11 (2011), pp.1740–1746.

[3] X. Ma et al., J. Microelectromech. Syst., 24 (2015), pp.1856–1867.

11:00 AM BM05.06.04

Multiplexed Single-Cell Secretomic Profiling on 3D Scaffolds Yao Lu; Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian, China.

Single cell barcode microchip (SCBC) has become an informative tool for comprehensive monitoring of the immune effector functions of single cells and has great value for quantifying cellular heterogeneity at the functional level in the complex biological systems such as the immune system or tumor microenvironment [1-4]. Despite its rapid progresses, efforts to control the three dimensional microenvironment for single cell measurements have been lacking [5]. We developed a simple method to incorporate three dimensional scaffolds with PDMS stencil into a multiplexed single cell secretomic analysis platforms to mimic the extracellular physical matrix and mechanical support for single cells [6]. Applying this platform to brain tumor cell line U87 to investigate single cell protein secretion behavior on different substrates, we revealed that single cell protein secretions were regulated differently in 3D microenvironments. The finding was further verified with intracellular cytokine staining, highlighting the significance of 3D single cell microenvironments. This new single cell biomimetic platform can be easily adaptable to other single cell assays and may become a broadly applicable three dimensional single cell analysis system to study the effect of microenvironment conditions on cellular functional heterogeneity *in vitro*.

References

[1] Seder RA, Darrah PA, & Roederer M (2008) Nature Reviews Immunology, 8(4):247-258.

[2] Chattopadhyay PK, Gierahn TM, Roederer M, & Love JC (2014) Nature immunology, 15(2):128-135.

[3] Lu Y, et al. (2013) Analytical Chemistry, 85(4):2548–2556.

[4] Lu Y, et al. (2015) PNAS, 112(7):E607-E615.

[5] Lu Y, et al. (2017) Lab on a Chip, 17(7):1250-1263.

[6] Lu Y, et al. (2018) Analytical Chemistry, 90, 5825–5832.

11:15 AM BM05.06.05

Integrated Measurement of Cytosolic Proteins and Transcripts in Single Cells Alexander Xu^{1,2}, Qianhe Liu¹, Kaitlyn Takata¹, Sarah Jeoung¹, Yapeng Su¹, Igor Antoshechkin¹, Sisi Chen¹, Matthew Thomson¹ and James Heath^{1,2}; ¹California Institute of Technology, Pasadena, California, United States; ²Institute for Systems Biology, Seattle, Washington, United States.

Single cell measurements have revamped our understanding of biological tissues by resolving their single cell heterogeneity. New technologies such as droplet microfluidic transcriptomics and microchip proteomics provide better insights on how healthy tissues function, and how aberrant cells in the tissue cause disease. However, our understanding of how the single cells in a tissue perform their functions is limited by the types of information that can be captured from each cell.

Here we present a method for measuring the whole transcriptome and cytosolic proteins in single cells on a microfluidic chip. By coupling single cell barcode chip (SCBC) proteomics and bead-based sequencing technologies, we capture multiple measurements of a single cell without splitting cell contents, and we use gold standard measurement modes – fluorescence sandwich immunoassays for proteins and sequencing for transcripts. This technique is enabled by a DNA labeling strategy that allows measurements to be taken independently and robustly, and linked after data processing.

We measure two cell types, showing that there is a unique molecular signature for both cell types in both protein and transcript data. The microfluidic chip is designed such that location barcodes scale geometrically and the chip can be readily scaled to produce larger single cell integrated datasets. This strategy for taking multiple measurements from single cells is unique in that it does not require either the protein or transcript signal to be converted from its native measurement mode. This is done in an effort to produce the best possible data using established technology. By using established technology, we are also able to further modify the integrated SCBC to capture metabolomic measurements in the future. Ultimately, this technology presents a generalizable DNA encoding strategy to augment sequencing methods, as well as a powerful tool to better understand single cell biology by expanding the scope of their measurements.

11:30 AM BM05.06.06

Ultra-Small Biocompatible Iron Oxide T₁ MRI Contrast Agents with Reduced Magnetic Coupling Fabian H. Starsich¹, Christian Eberhardt², Kerda Keevend³, Andreas Boss², Ann Hirt¹, Inge Herrmann³ and Sotiris E. Pratsinis¹; ¹ETH Zurich, Zurich, Switzerland; ²Institute of Diagnostic and Interventional Radiology, University Hospital Zürich, Zurich, Switzerland; ³Department Materials Meet Life, Swiss Federal Laboratories for Materials Science and Technology (Empa), Zurich, Switzerland.

Contrast agents are essential to magnetic resonance imaging (MRI) for the evidential visualization of soft tissue pathologies in regenerative medicine. MRI can be categorized into T₁- and T₂-weighted sequences that require as contrast agents paramagnetic and superparamagnetic materials, respectively. Typically, T₁-weighted MRI is preferred over T₂- due to the faster data acquisition using gradient-echo sequences and sharper image analysis. Commonly used and FDA-approved T₁ contrast agents are based on highly paramagnetic Gd complexes. Although very efficient in terms of contrast enhancement, these complexes have been associated with nephrogenic systematic fibrosis due to Gd³⁺ release, especially in long and repeated exposure scenarios. Here, ultra-small iron oxide nanocrystals co-oxidized with SiO₂ are investigated as a biocompatible alternative. By using SiO₂ as a spacing material, the effective magnetic size of iron oxide is reduced resulting in significant T₁ contrast enhancement due to minimized magnetic coupling. The nanocrystals are produced by scalable and sterile flame aerosol technology with potential production rates up to kg h⁻¹. The optimized FeO_x/SiO₂ nanoparticles attain comparable relaxivities to harmful Gd-complexes, however, with no apparent cytotoxicity at clinically relevant concentrations tested *in vitro* against four different cell types (PC3, HepG2, THP-1 and red blood cells). With this, these flame-made ultra-small iron oxide nanoparticles offer safe and efficacious access to T₁ contrast agents fulfilling major prerequisites for a future translation into clinics.

[1] Penfield, J. G.; Reilly, R. F. What Nephrologists Need to Know about Gadolinium. *Nat. Clin. Pract. Nephrol.* **2007**, *3*, 654–668.

[2] Starsich, F. H. L.; Sotiriou, G. A.; Wurnig, M. C.; Eberhardt, C.; Hirt, A. M.; Boss, A.; Pratsinis, S. E. Silica-Coated Nonstoichiometric Nano Zn-Ferrites for Magnetic Resonance Imaging and Hyperthermia Treatment. *Adv. Healthc. Mater.* **2016**, *5*, 2698–2706.

SESSION BM05.07: Breakthrough Technologies for In Vitro Tissue Modeling

Session Chairs: W. Swieszkowski and Yu Shrike Zhang

Thursday Afternoon, November 29, 2018

Sheraton, 2nd Floor, Liberty C

1:30 PM *BM05.07.01

Infections and Inflammation-on-a-Chip—Neutrophil Swarming Against Fungi D. Irimia; Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States.

Neutrophil swarms protect us from microbes by sealing off sites of infection. In the absence of swarming, microbes could invade into healthy tissues, and severe infections could progress. Recent observations in animal models have shown that neutrophil swarming is one essential immune response against large microbes and clusters of microbes. Although relevant, such models are low throughput and are also too complex to allow for the precise dissection of the innate immune actions that protect against infections. Large microscale arrays of targets for the study of human neutrophils during swarming *ex vivo* provide an attractive alternative and enable the observation of thousands of swarms at once against live-microbe. Moreover, the synchronized swarming in small volumes enables the detailed analysis of the amount and timing of mediators released during human-neutrophil swarming, responsible for the early acceleration and late resolution of the process. In the clinical setting, we compared the swarming behavior of neutrophils from patients following major trauma and healthy individuals and found various deficiencies that resolve over time. The new technologies for studying Infections and Inflammation-on-a-chip represents a valuable discovery and screening platform, which could lead to novel anti-inflammatory and anti-microbial treatment strategies.

2:00 PM *BM05.07.02

Biofabrication of Biomimetic 3D Models of Musculoskeletal Tissues W. Swieszkowski¹, M. Constantini^{1,2}, Chiara Rinoldi¹, J. Idaszek¹, A. Kosik-Koziol¹ and E. Kijenska-Gawronska¹; ¹Faculty of Materials Science and Engineering, Warsaw University of Technology, Warsaw, Poland; ²Institute of Physical Chemistry, Polish Academy of Sciences, Warsaw, Poland.

An innovative technique that may overcome current limits in reproducing complex structures of human tissues and organs is 3D biofabrication. This emerging fabrication technology relies on the simultaneous deposition of cells and biomaterials, mostly in a layer-by-layer fashion, to form 3D well-

organized living heterogeneous porous structures that can mirror physiologically and morphologically relevant complex biological architectures. In this study, we present an innovative strategy to biofabricate biomimetic 3D models of musculoskeletal tissues, like muscle, tendon, or cartilage. Our 3D biofabrication approach is based on a microfluidic system coupled to a co-axial needle extruder for high-resolution computer-controlled 3D deposition of hydrogel fibers laden with different cells. By formulating tailored hydrogel based bioinks and precisely controlling the 3D spatial organization of the extruded hydrogel fibers, it was possible to biofabricate advanced engineered living constructs mimicking natural musculoskeletal tissues. Furthermore, the influence of mechanical loading and biochemical stimulation on proliferation, alignment, and differentiation of the cells as well as ECM deposition in 3D biofabricated constructs will be discussed. Additionally, the preliminary in vivo performance of selected 3D biomimetic 3D tissue models will be presented.

2:30 PM *BM05.07.03

Engineered Tumor Ecosystem for Personalized Anti-Cancer Therapy S. Sengupta; Division of Engineering Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, Massachusetts, United States.

Being able to select the most effective therapy for each individual cancer patient remains the Holy Grail in cancer treatment. In today's precision medicine, this selection is made based on molecular and genetic profiling of biomarker expression. However, a biomarker often does not translate into a successful clinical response to the selected therapy. We have engineered a 'micronized tumor ecosystem' that conserves the patient tumor characteristics with high fidelity, and integrated with a novel machine learning algorithm can accurately predict anticancer drug responses. This talk will discuss how such a micronized tumor ecosystem can be used to choose the most effective therapy for a patient before initiation of treatment.

3:00 PM BREAK

3:30 PM *BM05.07.04

Origami Microfluidics for Biomimetic Organs on a Chip C. Livermore^{1,2,3}; ¹Department of Electrical and Computer Engineering, Northeastern University, Boston, Massachusetts, United States; ²Department of Mechanical and Industrial Engineering, Northeastern University, Boston, Massachusetts, United States; ³Northeastern University, Boston, Massachusetts, United States.

Fluid mechanics at the shortest length scales enables many functions of life, such as microcirculation in the human body and transpiration in plants. Ideally, we would be able to translate these properties directly into engineered tissues and organ on a chip systems, but there remains a significant gap between the materials and techniques of conventional microfluidics and the functions of the human body. For example, conventional organs on a chip can struggle to replicate the massively parallel flow and perfusion architecture of the liver. Origami-based microfluidics offer a new paradigm for addressing these challenges. Folding offers a low-cost, rapid means of creating flow structures to mimic vasculature. Multi-material architectures enable additional transport via diffusion, and directed assembly of cells offers hierarchical structure at the smallest length scales. This talk will present the enabling tools of origami tissue engineering, including the use of origami-based techniques to create multi-material, flow/perfusion microfluidic devices as a platform for scalable tissue engineering. In particular, the presentation will focus on the application of these multifunctional systems for the design, fabrication, and characterization of origami liver tissue units.

4:00 PM *BM05.07.05

Putting 3D Bioprinting to the Fabrication of Tissue Models Yu Shrike Zhang; Division of Engineering Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Cambridge, Massachusetts, United States.

The talk will discuss our recent efforts on developing a series of bioprinting strategies including sacrificial bioprinting, microfluidic bioprinting, and multi-material bioprinting, along with various cytocompatible bioink formulations, in facilitating the fabrication of biomimetic 3D tissue models. These platform technologies, when combined with bioreactors and bioanalysis, are anticipated to provide new opportunities for constructing functional microtissues with a potential of achieving improved drug screening and precision therapy by overcoming certain limitations associated with conventional models based on planar cell cultures and animals.