



# Biomaterials Day

Case Western Reserve University  
October 26, 2013

Co-organized by Case Western Reserve University, the University of Kentucky, and Purdue University

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Society For Biomaterials





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## WELCOME

On behalf of Case Western Reserve University, the University of Kentucky, and Purdue University, we would like to thank you for joining us for the 5<sup>th</sup> Annual Biomaterials Day in Cleveland, Ohio. Over 150 scientists and engineers from over ten institutions are pre-registered.

Generous support from the Society For Biomaterials, the Case School of Engineering, the Provost of Case Western Reserve University, CWRU Undergraduate Student Government as well as our industry sponsors DiaPharma, Athersys Inc., Steris, and Bose have made this event free for all registrants.

We are pleased to introduce a broad program of oral and poster presentations covering a range of materials and applications, with the additional honor of having Dr. Lynne C. Jones give the keynote address. There will be multiple opportunities for networking with colleagues, including morning and afternoon poster sessions and lunch. Don't forget to stop by the exhibitor booths in the ballroom throughout the day. We look forward to engaging interactions!

Sincerely,

Nicholas P. Ziats, Ph.D.  
Advisor to Chapter  
President-elect of SFB

Anirban Sen Gupta, Ph.D.  
Advisor to Chapter

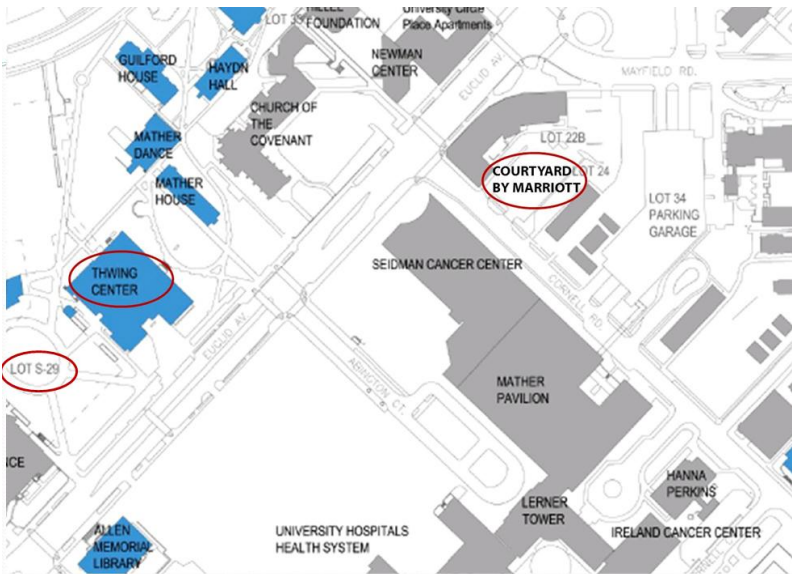
Christa L. Modery-Pawlowski  
President of Chapter  
Biomaterials Day Coordinator

Lydia M. Everhart  
Biomaterials Day Coordinator

## SCHEDULE OF EVENTS

<b>Time</b>	<b>Spartan Room</b>	<b>1914 Lounge</b>
8:30 am	<b>Registration/Poster Setup – Ballroom</b>	
9:00 am	<b>Opening Session – Ballroom</b>	
9:30 am	Rebecca Scott	Dr. Jessica Sparks
10:00 am	Lei Kerr	Derek Jones
10:15 am	Prachi Gupta	David Cantu
10:30 am	<b>Break</b>	
10:45 am	Dr. Jason DeRouchey	Dr. Alan Litsky
11:15 am	Gregory Howard	M. Jane Brennan
11:30 am	Paul Chariou	Kelsey Potter
11:45 am	<b>Poster Session - Ballroom</b>	
12:30 pm	<b>Industry Luncheon - Ballroom</b>	
1:15 pm	<b>Keynote Lecture: Dr. Lynne Jones - Ballroom</b>	
2:15 pm	Dr. Ariella Shikanov	Dr. Jeffrey Capadona
2:45 pm	Han Shih	Young Jo Kim
3:00 pm	Christopher Mosher	Matt Brown
3:15 pm	<b>Poster Session – Ballroom</b>	
4:00 pm	Madhumitha Ravikumar	Andrew Sylvester
4:15 pm	Hangyu Zhang	Andrew Vasilakes
4:30 pm	Kyle Kovach	Victor Pan
4:45 pm	<b>Awards, Closing Talks – Ballroom</b>	

## CAMPUS MAP:



## PARKING:

Parking is available in Lot S-29 (see map above) during the Biomaterials Day events. Ask the attendant for a receipt upon exiting the garage, and we can offer reimbursements for parking costs.

**KEYNOTE ADDRESS:**

**Putting the Bio into Biomaterials**



*Lynne C. Jones, PhD, MS  
Associate Professor of  
Orthopaedic Surgery  
Johns Hopkins University*

Lynne C. Jones, Ph.D., M.S., is an Associate Professor of Orthopaedic Surgery with a joint appointment in the Department of Materials Science and Engineering at the Johns Hopkins University. She received her B.S. from Ursinus College, a Master's Degree from Towson State University; and a Doctorate Degree from John Hopkins University. Academically, she holds positions as the Director of Orthopaedic Resident Research, Director of the Center for Osteonecrosis Research and Education, and the Technical Director of the Arthritis Surgery Bone Bank. She has published over 100 peer-reviewed publications and has been the keynote speaker at international meetings speaking on her research areas of interest – osteonecrosis, total joint arthroplasty, and bone grafting – as well as on teamwork and communication. She has received a number of awards for her research and was elected as a Fellow of the International Union of Societies - Biomaterials Science and Engineering and as a Fellow of the American Institute for Medical and Biological Engineering. She was the second female selected for the prestigious Hip Society. Dr. Jones has mentored over 100 undergraduate, graduate, medical, residents and fellows in both basic and clinical orthopaedic research. Dr. Jones has over 35 years of active orthopaedic research, and is a member of numerous prestigious national and international societies. She served as President of the Society for Biomaterials in 2009-2010 and is currently President-elect of ARCO-International and the Secretary/Treasurer for the National Osteonecrosis Foundation. She is a basic science member of the American Association of Orthopaedic Surgeons and a Board member of the Rocky Mountain Bioengineering Symposium. In addition to her academic and research life, she is also active with her family, church and the community



## **INVITED SPEAKER**



*Alan S. Litsky, M.D., Sc.D.  
Associate Professor of  
Orthopaedics and  
Biomedical Engineering  
The Ohio State University*

### **Dandelions as a Model for BioEngineered Tendons**

Prof. Alan S. Litsky is an associate professor with a joint appointment in the Department of Orthopaedics and the Department of Biomedical Engineering at Ohio State University where he also serves as director of the Orthopaedic BioMaterials Laboratory. He earned an undergraduate degree in Chemistry from Princeton University, a medical degree from Columbia University's College of Physicians and Surgeons, and his Sc.D. in Materials Science and Engineering from M.I.T. His primary research focus is hard-tissue biomaterials including new materials for orthopaedic, dental, and veterinary applications. Dr. Litsky's courses focus on biomaterials, tissue mechanics, and research ethics.

Research in the Orthopaedic BioMaterials Laboratory includes the investigation of shape-memory alloys for fracture fixation, a quantification of the micromotion between components of total hip arthroplasties, studies of the fatigue behavior of external fixators and dental prostheses, and testing a novel technique for securing mechanical devices to skeletal muscle which is being used for the development of a synthetic tendon. Another project focuses on gathering force-motion data of bone cutting tools which will provide input to improve the haptic feedback of a surgical simulation system. Clinically-driven projects have focused on fracture fixation techniques, intra-articular knee stresses, and the mechanics of osteochondral plugs and ACL graft fixation.

Prof. Litsky is an active member of the Orthopaedic Research Society and the Society for Biomaterials, and is a fellow of the American Institute of Medical and Biological Engineering. He currently chairs the University's Conflict of Interest Policy Committee and serves on the governing board of the Society for Biomaterials.

## **INVITED SPEAKER**



*Ariella Shikanov, Ph.D.  
Assistant Professor of  
Biomedical Engineering  
University of Michigan*

### **Natural and Synthetic Hydrogels for Engineering the Ovarian Follicle Environment**

The research in Shikanov lab aims to create artificial constructs that direct tissue regeneration and restore biological function by combining approaches from engineering, materials, chemistry and life sciences. To achieve this, we use natural hydrogels and multifunctional synthetic hydrophilic polymers. The main application realms of our research are tissue engineering and reproductive toxicology. We address the challenges to sustain a functioning tissue culture by designing tunable and functional hydrogels that support and direct biological functions. Our goal is to develop and implement new strategies for tissue engineering and regenerative medicine, as well as developing new approaches for in vitro high throughput screening to test and predict the reproductive toxicological effect of substances and their effect on follicle health and development.

Ariella Shikanov joined the Department of Biomedical Engineering at the University of Michigan in Fall 2012 as an Assistant Professor. She completed a postdoctoral fellowship at Northwestern University in Chicago in a multidisciplinary collaboration called the Oncofertility Consortium, which was created to address the infertility induced by chemotherapy in cancer survivors. She developed an inter-penetrating network (IPN) of fibrin and alginate to create a mechanically dynamic environment that allows ovarian follicle to grow during culture and prevents compressive stress from accumulating on the follicle as it expands into the hydrogel. This work was followed by development of the first synthetic follicle culture system based on polyethylene glycol hydrogels crosslinked by proteolytically degradable peptides

## **INVITED SPEAKER**



*Jason DeRouchey, Ph.D.  
Assistant Professor of  
Chemistry  
University of Kentucky*

### **Understanding DNA Condensation: From Simple Ions to Packaging in Sperm**

Jason DeRouchey is an Assistant Professor in the Department of Chemistry at the University of Kentucky. He received his B.S. degree in Chemistry from the University of Texas at Dallas in 1996. Professor DeRouchey then obtained a MS and PhD in Polymer Science and Engineering at the University of Massachusetts-Amherst with Thomas P. Russell. He first began working with questions of dynamics and DNA as a Alexander von Humboldt Fellow working with Joachim Rädler at the Institute of Experimental Physics at the Ludwig Maximilians Universität (LMU) Munich. Dr. DeRouchey then joined the Laboratory of Physical and Structural Biology at the National Institute of Child Health & Human Development (NICHD) at the National Institutes of Health (NIH) as a IRTA fellow working with V. Adrian Parsegian. Currently, the DeRouchey laboratory is broadly interested in understanding the forces, structures, and dynamics that govern protein-protein and protein-DNA interactions to address problems in biology and biomedicine. Learning the strength, specificity, and reversibility in associates of biologically important macromolecules, typically in crowded environments, is crucial to our understanding of gene and cellular function and for effective and rational drug design.

## INVITED SPEAKER



*Jeffrey Capadona, Ph.D.  
Assistant Professor of  
Biomedical Engineering  
Case Western Reserve  
University*

### Strategies to 'Rewire' the Neuro-inflammatory Response to Intracortical Microelectrodes

Dr. Capadona was born in 1978 in the southwest suburbs of Chicago, IL. He attended Saint Joseph's College in Rensselaer, IN on an academic and athletic scholarship. In May 2000, Dr. Capadona received his B.S. in Chemistry and moved to Atlanta, GA to attend Georgia Institute of Technology. In 2005, Dr. Capadona completed his Ph.D. thesis studying the effects of surface properties of biomedical implants on the control of cellular response and function. In June of 2005, Dr. Capadona began his career with the Department of Veterans Affairs as a Research Health Scientist. At this point, Dr. Capadona became interested in the neurodegenerative response to implanted biomedical devices. Since joining the VA, Dr. Capadona has received an Associate Investigator Award, a Career Development Award II, and is currently the PI of a Rehabilitation R&D Merit Review. In August 2010, Dr. Capadona began a tenure track appointment in the Department of Biomedical Engineering at Case Western Reserve University. Dr. Capadona has co-authored two patents, two book chapters, ~95 scientific abstracts and over 28 peer reviewed scientific manuscripts, including one in *Science* and another that received the cover of *Nature Nanotechnology*. Dr. Capadona's research articles have been cited over 1700 times. His recent awards include: the Case School of Engineering Faculty Research Award, multiple graduate student mentoring awards, and the 2011 Presidential Early Career Award for his work on the development of bio-inspired materials for long-term implantable neurological devices at the Department of Veterans Affairs, under the umbrella of Rehabilitation R&D.

The Capadona Lab applies principles of material science, biochemistry, bio-mimicry, and neuroscience to better understand the neuroinflammatory response to devices implanted in the central nervous system. Many of the approaches currently under exploration in the Capadona Lab will be presented. A focus will be placed on developing clinical solutions that could be rapidly translated to facilitate clinical care for patients with existing CNS technologies.

## **INVITED SPEAKER**



*Jessica L. Sparks, Ph.D.  
Associate Professor  
Chemical, Paper, and  
Biomedical Engineering  
Miami University*

### **The Effects of Decellularization of Liver Mechanical Properties and Perfusion Dynamics**

Jessica Sparks received her Ph.D. in Biomedical Engineering from the Ohio State University (2007), where she was the recipient of the Distinguished University Fellowship Award for 2002 and 2007. She holds a B.S. degree from the University of Notre Dame in Pre-Medical Studies and Philosophy, and she earned a Master's degree in Anatomy from the Ohio State University. Dr. Sparks was a faculty member of the Biomedical Engineering Department at Wake Forest School of Medicine from 2007 to 2012. During this time she also held a primary faculty appointment in the Virginia Tech – Wake Forest University School of Biomedical Engineering and Sciences. Dr. Sparks recently joined Miami University as an Associate Professor in August 2012. She is actively engaged in teaching and research activities in the new Bioengineering program. Her current research includes liver mechanobiology, computational modeling of interstitial flow in liver and in tissue engineering scaffolds, and designing biomechanically realistic anatomical models (patient simulators) for multidisciplinary surgical team training. She is a member of the American Society of Mechanical Engineers, the Biomedical Engineering Society, the Association for Surgical Education, and the Society for Simulation in Healthcare.

## INVITED SPEAKER



*Rebecca Scott  
Graduate Student  
Biomedical Engineering  
Purdue University*

### Development of Localized Antithrombotics for the Treatment of Restenosis

Over the past 10 years, the number of percutaneous coronary interventions (PCI) performed in the United States has increased by 33%, thrombosis, neointimal hyperplasia, and restenosis remain complications of this procedure and inhibit complete functional recovery of the vessel wall. While a wide range of anti-restenotic therapeutics has been developed, many elicit non-specific effects that compromise vessel healing. Drawing inspiration from biologically-relevant molecules, our lab developed a mimic of the natural proteoglycan decorin, termed DS-SILY, which can mask exposed collagen and thereby effectively decrease platelet activation, thus contributing to suppression of vascular intimal hyperplasia. Recently, we investigated the effects of DS-SILY on human smooth muscle cells (SMCs) to evaluate the potential impact of DS-SILY-SMC interaction in restenosis. DS-SILY decreased SMC proliferation, migration, protein synthesis, and pro-inflammatory cytokine secretion *in vitro* in a concentration dependent manner, as compared to both untreated and growth factor-stimulated controls. Furthermore, we are investigating the delivery of biologically active DS-SILY released from water-soluble polymer films developed within our laboratory. *In vivo* delivery of DS-SILY decreased platelet activation, as well as reduced neointimal hyperplasia by 60%, in Ossabaw swine. These results indicate that DS-SILY demonstrates multiple biological activities that may all synergistically contribute to an improved treatment paradigm for balloon angioplasty.

Becca Scott received her Bachelor's degree from Saint Louis University in Biomedical Engineering. She is currently a PhD candidate in the Weldon School of Biomedical Engineering at Purdue University. Her research focuses on developing biomaterials for drug delivery towards the treatment of cardiovascular disease. Becca received the 2010 Undergraduate Research Award from the Society of Biomaterials and is currently an NSF graduate research fellow. She also currently serves as the Student Representative for the Biomedical Engineering Society Board of Directors.

## **POSTER PRESENTATION PROGRAM**

(alphabetical by first name)

<b>Poster #</b>	<b>Presenter and Title</b>
28	<b>Aaron Kosinski</b> <i>Characterization of a Dynamic PLGA Core + pNIPAM Shell Nanoparticle System for Targeted Drug Delivery Applications</i>
10	<b>Aditya Balasubramanian</b> <i>Rapid stiffness transitioning material designs for biomedical devices</i>
7	<b>Amy M. Wen</b> <i>Enhanced Delivery of PAI-1 Antagonist for Thrombolysis using Elongated Viral Nanoparticles</i>
32	<b>Charles W. Peak</b> <i>Degradable Hydrogels from Poly(ethylene glycol)-Poly(L-lactic acid) and Collagen Networks</i>
16	<b>Congcong Zhu</b> <i>Light-Induced Remodeling of Physically Crosslinked Hydrogels Using Near-IR Wavelengths</i>
8	<b>Crystal Shin</b> <i>Development of in vitro Three-dimensional Tumor Model</i>
2	<b>Edgardo Rivera</b> <i>Local delivery of Silibinin from beta-cyclodextrin polymers for the treatment of solid tumors</i>
39	<b>Emma Headley</b> <i>Enhanced Osteogenic Differentiation of Adipose-Derived Stem Cells in Growth Factor Presenting Gelatin Hydrogels</i>
33	<b>Fei Lin</b> <i>Post-electrospinning "Click" Modification of Degradable Amino Acid-based Poly(ester urea) Nanofibers</i>
11	<b>Haefa Mansour</b> <i>Development of Adhesive Elastomeric Proteins for Surgical Adhesive Applications</i>
4	<b>Haoyan Zhou</b> <i>Non-invasive characterization of polymer degradation using ultrasound elastography (UE)</i>
3	<b>Huiying Jia</b> <i>Sustained Ibuprofen Release Using Composite Poly(Lactic-co- Glycolic Acid)/Titanium Dioxide Nanotubes from Ti Implant Surface</i>

29	<b>James Cole</b> <i>Responsive nanoparticles of elastin like polypeptides for theranostic applications</i>
6	<b>James McMasters</b> <i>Targeted Thermoresponsive Nanoparticles for Treatment of Atherosclerotic Vascular Disease</i>
19	<b>Jaqueline Diane Wallat</b> <i>The Tobacco Mosaic Virus as a Scaffold for Smart Polymer Nanoparticles</i>
15	<b>Jennifer L. Kahn</b> <i>Collagen matrix templating for increased nano and microstructure of silica thin layers deposited at the cell surface</i>
14	<b>Jessica Nguyen</b> <i>The Neuroinflammatory Response to Mechanically-Adaptive Polymer Implants</i>
5	<b>Jialu Yan</b> <i>Enzymatic Polyesterification to Produce Functionalized PLA and Poly(n-hydroxyalkanoic acid)s</i>
22	<b>John Hermann</b> <i>Disruption of Toll-like Receptor Signaling to Improve Tissue Integration of Intracortical Microelectrodes</i>
17	<b>Jordan Boivin</b> <i>Synthesis of Protein-Polymer Hybrid Materials Using Controlled Radical Polymerization</i>
27	<b>Karin L. Lee</b> <i>In vitro and In vivo Evaluation of the Immunogenic Properties of PEGylated Potato Virus X</i>
9	<b>Kihwan Kim</b> <i>New in vitro model for testing drug delivery into tumor tissue from capillary vessels in the tumor microenvironment</i>
25	<b>Lauren Randolph</b> <i>Targeting atherosclerotic plaques in vivo using rod-shaped tobacco mosaic virus</i>
26	<b>Lewis Tian</b> <i>Heteromultivalent Ligand Modification to Enhance Specific Bioactivity of Vascular Nanomedicine Platforms</i>
38	<b>Lin Lin</b> <i>Biomimetic Engineered Poly (ethylene glycol) Hydrogel for Smooth Muscle Cell Migration</i>



31	<b>Luke Klosterman</b> <i>Fabrication of compliant electrode by in situ silver film formation on hydrogel</i>
12	<b>Meredith Muskovich</b> <i>Hydrogel Templates for Ordered In situ Metallization</i>
30	<b>Michael McBurney</b> <i>Development of a deterministic antibody array display technology using a plant virus-based molecular scaffold</i>
40	<b>Nathan Millard</b> <i>Development of a Hydrostatic Pressure Chamber for Determining the Effect of Pressure on Liver Progenitor Cells</i>
37	<b>Nelda Vazquez-Portalatin</b> <i>Synthetic Peptidoglycan Lowers Friction Levels in Articular Cartilage Surface</i>
36	<b>Nida Tanataweethum</b> <i>Mechanical Property and Biocompatibility of PLLA/DCPD Composite 3D Scaffolds</i>
41	<b>Phuong Dang</b> <i>Guiding chondrogenesis and osteogenesis with hydroxyapatite and BMP-2 incorporated within a high-density hMSC system</i>
20	<b>Pitirat Pholpabu</b> <i>Regenerative Integration of Percutaneous Devices Using Macrophage Modulating Elastomers</i>
1	<b>Rebecca Scott</b> <i>Characterization and Delivery of Localized Antithrombotics for the Treatment of Restenosis</i>
23	<b>Ruth Herrera-Perez</b> <i>Scaffold composition alters the morphology and migration characteristics of glioblastoma stem cells in 3D culture</i>
13	<b>Shan Lu</b> <i>Electrospun Spider Silk Fibers Retain the Cyclical Humidity Response Observed in Natural Silk Fibers</i>
21	<b>Smrithi Sunil</b> <i>Characterization of Infiltrating Blood-Derived Cells Surrounding Intracortical Microelectrodes</i>
18	<b>Stephen Hern</b> <i>Shape matters: the diffusion rates of TMV rods and CPMV icosahedrons in a spheroid model of extracellular matrix are distinct</i>

24	<b>William Tomaszewski</b> <i>Disruption of Cluster of Differentiation 14 Signaling to Improve Intracortical Microelectrode Integration</i>
34	<b>Yiting Hao</b> <i>Visible light cured thiol-vinyl hydrogels with tunable degradation for 3D cell culture</i>
35	<b>Yuqian Chen</b> <i>Determining the Extent of Crosslinking in Resilin-based Hydrogels</i>

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## **ORAL PRESENTATION ABSTRACTS**

**Research Category:** Drug Delivery

**Andrew Vasilakes**

**Institution:** University of Kentucky

**Title:** Formation of a Covalently-Bonded Vancomycin Containing Hydrogel for Local Antibiotic Delivery

**Authors:** Andrew Vasilakes, Dr. David A. Puleo, Dr. J. Zach Hilt, Dr. Thomas D. Dziubla

One method of controlling surgical site infection is to provide controlled release of antibiotics. However, once the antibiotic payload is depleted, the remaining vehicle can become a scaffold supporting the colonization of bacterial biofilms, enhancing site infection which can become potentially life threatening. Secondary surgeries are typically performed as a means of preventing this type of infection. To maintain the effectiveness of a locally delivered antibiotic biomaterial without the drawback of a required second surgery, we propose a hydrogel drug delivery system in which the drug release rate of vancomycin and degradation rate of the hydrogel are bound via covalent-incorporation of vancomycin in the hydrogel backbone. The free primary-amine of vancomycin was utilized in a Michael-Addition reaction as a partial substitute to isobutylamine in reaction with PEGDA and DEGDA to form a poly( $\beta$ -amino ester) hydrogel. Covalent-addition of vancomycin was corroborated through detection of unique HPLC peaks and detection of an increased vancomycin m/z via mass spectroscopy. Further, comparison of vancomycin release rate to degradation rate indicated a strong correlation between degradative release, a feature not seen with free loaded vancomycin which is diffusion controlled. While the vancomycin molecule was modified to contain additional carboxylic acid groups, we determined that it was still antimicrobially active upon *Staphylococcus aureus*; this activity was shown to be present in HPLC retention-time fractions where free-vancomycin was not present in controls. Against planktonic *S. aureus*, the MIC<sub>90</sub> of HPLC-fractionated vancomycin-containing hydrogel degradation products was 155  $\mu\text{g/mL}$ , whereas the MIC<sub>90</sub> for fresh vancomycin was 2  $\mu\text{g/mL}$ .

## **Prachi Gupta**

**Institution:** University of Kentucky

**Title:** Single Phase Reaction-Precipitation System to Synthesize Anti-oxidant conjugated Poly ( $\beta$ -Amino Ester) Nanogels

**Authors:** Prachi Gupta, Dr. Thomas Dziubla, Dr. J. Zach Hilt

Poly ( $\beta$ -Amino Esters) (PBAE) are a class of versatile, pH sensitive, hydrolytically biodegradable polymers with tunable degradation and release properties. These polymers have shown a great potential as a matrix for gene and small molecule drug delivery via classic drug encapsulation/formulation approaches. Moreover, PBAE can act as polymeric prodrug carriers, wherein active agents (e.g., curcumin, quercetin) can be acrylated and subsequently conjugated into the polymeric backbone of the resulting hydrogel, greatly enhancing the release rate and providing a mechanism for stabilizing highly labile drugs. Formulating these polymeric systems into nanoparticles would allow the drug to be administered through various routes like intravenous injections, oral administration, would reduce renal clearance and can be surface modified for targeted delivery. However, owing to the high reactivity of the monomers and stability concerns of the ensuing particles, standard oil-water nano-emulsion methods are not adaptable for their formation. Further, nano-precipitation, when done in two immiscible organic solvent suspension systems, can lead to aggregation and instability during the purification processes. In this work, a novel approach to formulate anti-oxidant conjugated nanogels in a single-phase organic system is explored where two multifunctional monomers react with each other and form stable nanogel/nanoparticle suspension. In the present research, quercetin was used as the molecule of interest as it possesses strong anti-oxidative, anti-inflammatory and anti-cancerous properties but has poor water solubility and is structurally unstable in aqueous systems. To formulate nanoparticles/nanogels (NGs), quercetin multiacrylate (QMA) was reacted with a low molecular weight secondary diamine (DA) in acetonitrile via a Michael addition reaction to form a cross-linked polymeric nanoparticle suspension. Subsequently strategies for pegylation of obtained nanogels were evaluated to enhance their stability and stealth characteristics.. Yield of crosslinking reaction varied from 83-97% and nanogels obtained were in the size range of 200-650nm determined using SEM and DLS. These nanogels showed continuous and uniform released of active quercetin in PBS for 40 hours under physiological conditions (37°C, pH=7.4) as determined using HPLC and UV-Vis spectroscopy and Trolox equivalent antioxidant capacity assay. Radiolabeling studies showed decreased protein (IgG) binding towards the PEG coated particles adding to the increased stability benefit..

**Matt Brown****Institution:** University of Kentucky**Title:** Lysostaphin as an effective anti-biofilm agent against *Staphylococcus aureus* biofilms and its potential biomaterial applications**Authors:** Matt Brown, Gus Huerta, Tyler Fields, Rebecca Peayala, Dr. Todd Milbrandt, Dr. Tom Dziubla, Dr. Dave Puleo

A biofilm is a community of bacterial cells that are no longer in a planktonic state and have attached themselves to each other and another surface, such as materials implanted within the body. These infections are difficult to treat clinically and can cause increased hospital stays, costs, or failure of implanted devices. Vancomycin, which is one of the more commonly used antibiotics for treating *Staphylococcus aureus* (*S. aureus*), was able to inhibit biofilm formation at concentrations as low as 5  $\mu\text{g/ml}$  but was unable to disrupt an existing biofilm at concentrations as high as 2000  $\mu\text{g/ml}$ . Lysostaphin is an endopeptidase that has been shown to both inhibit and disrupt bacterial biofilms by cleaving the crosslinks in the cell walls of *Staphylococcus* spp., killing bacterial cells and preventing biofilm formation. In the present in vitro studies, lysostaphin was shown to be able to inhibit and disrupt *S. aureus* biofilm formation at concentrations as low as 10  $\mu\text{g/ml}$ . When loaded into poly(lactic-co-glycolic acid) (PLGA) microspheres a sustained release of lysostaphin can be achieved for over a week in vitro. The ability to load lysostaphin into a delivery vehicle further increases its potential therapeutic effectiveness by allowing for controlled release over time in a biomaterial device. The success of these initial trials warrants further investigation into the ability of lysostaphin to inhibit and disrupt biofilm formation after being incorporated into a therapeutic biomaterial.

**Andrew Sylvester****Institution:** Cleveland Clinic**Title:** Polymeric Nanoparticles for Modulated Clot Lysis in Abdominal Aortic Aneurysms (AAAs)**Authors:** Andrew Sylvester, Balakrishnan Sivaraman, Anand Ramamurthi

Abdominal aortic aneurysms (AAAs) are one of the leading causes of death in the United States, and are typically associated with the upregulation of matrix metalloproteinases (MMPs) -2 and -9 in the aortic wall. An intraluminal thrombus (ILT) is commonly present in close proximity to the AAA wall, through which blood continues to flow, and plays an important role in AAA progression on account of it serving as a reservoir of inflammatory cells and proteases (including MMP-2 and -9). There is a critical need for highly modulated lysis of the ILT to avoid systemic thrombotic & thromboembolic effects, while concurrently minimizing the adverse effects of the proteases from the ILT, as well as hypoxia, in mediating further AAA progression. NPs formulated functionalized with didodecyldimethylammonium bromide (DMAB; cationic NPs) demonstrated controlled tissue plasminogen activator (tPA; thrombolytic agent) release and a more modulated clot lysis profile compared to those formulated with polyvinyl alcohol (PVA; anionic NPs). The effective NP-based tPA dose required for clot lysis was nearly 5-fold lower than the exogenous tPA dose. Additionally, DMAB-NPs demonstrated 1.75-fold higher clot binding efficiency compared to PVA-NPs. Based on MMP-2 synthesis data there was no significant difference between the control clot and the cases where the clot was lysed with 0.5 mg/mL of either DMAB or PVA NPs containing tPA. Suitable NPs would be expected to be those which demonstrate minimal clot lysis time and/or lowest tPA loading & release required for clot lysis, as well as decreased MMP activity in cell culture.

**Lei Kerr**

**Institution:** Miami University

**Title:** Kinetic of pH dependent Drug Release from Drug Carrier of Composite of polymer/TiO<sub>2</sub>

**Authors:** Lei Kerr, Huiying Jia

TiO<sub>2</sub> nanotubes have a great potential to be used as drug delivery carriers due to their high surface area, strong chemical stability and ability to promote bone growth. Incorporating polymer into TiO<sub>2</sub> nanotubes has been found to be able to dramatically improve drug release time from hours in pure TiO<sub>2</sub> nanotubes to several days. However, the kinetics of drug release in this type of polymer/TiO<sub>2</sub> nanotubes composite structure is not well understood. The drug release profile varies with the types of drugs and is pH dependent. In this study, lidocaine and carprofen were selected as model drugs to represent weak base and weak acid drugs, respectively. Poly(lactic co glycolic acid) (PLGA) is a FDA approved widely used biodegradable polymer and thus was chosen in this study. Mathematic models used to fit the in vitro drug release experimental data indicate that at higher pH, the drug release was first order diffusion controlled and at lower pH, the release of the two drugs exhibits two staged controlled release mechanism. The first phase is due to drug diffusion and the second stage is a result of PLGA polymer degradation. In addition, the rate of drug release from polymer/TiO<sub>2</sub> drug carrier was mainly controlled by three pH dependent factors: the solubility of the drug, the degree of polymer swelling/degradation and the electrostatic force between polymer and drug. This study suggests that controlled release could be achieved for polymer/TiO<sub>2</sub> drug carrier via the modulation of pKa values of polymers and drug solubility.



**Victor Pan****Institution:** Case Western Reserve University**Title:** Platelet-Inspired Nanovehicles for Targeted Delivery of Doxorubicin to Metastatic Breast Cancer**Authors:** Victor Pan, Christa Modery-Pawłowski, Alyssa Master, Preethi Siva, Gregory Howard, Dr. Anirban Sen Gupta

Tumor metastasis occurs when cancer cells dislodge from a primary tumor and migrate to other sites in the body to form secondary colonies. Recent literature has revealed that a metastasizing cancer cell's ability to travel efficiently through the circulatory system, as well as, its adhesion to a distal site and subsequent proliferation into a metastatic colony, can be effectively mediated by blood platelets through ligand-receptor based cell-trafficking and pro-metastatic signaling. Rationalizing from such mechanistic possibilities of platelet-cancer cell interactions, we have investigated the expression of platelet-interactive receptors on MDA-MB-231 (pro-metastatic) versus MCF-7 (low-metastatic) human breast cancer cells. Subsequently, we have engineered liposome-based platelet-inspired synthetic vehicle constructs that can mimic the relevant molecular binding interactions between platelets and metastatic cancer cells and have investigated their ability to target metastatic breast cancer cells at enhanced levels, compared to low-metastatic cells. Building on these studies, we encapsulated a model cancer drug (e.g. doxorubicin (DOX)) in our platelet-inspired particles and studied diffusive release of DOX under physiologically-relevant conditions. To evaluate their efficacy in vitro, we treated MDA-MB-231 cells with DOX-loaded platelet-inspired particles and measured cell viability via MTT assay, resulting in significant levels of cell killing compared to unmodified particles. These results establish the feasibility of utilizing platelet-inspired binding mechanisms for enhanced targeting of drug delivery platforms to metastatic cancer cells.

**Gregory Howard****Institution:** The University of Akron**Title:** Multifunctional Hybrid Nanoparticles as a Co-delivery System for RNAs and Chemotherapeutics**Authors:** Gregory Howard, Ki Young Choi, Oscar Ferreira Silvestre, Xiaoyuan Shawn Chen

RNA interference (RNAi) is an attractive option for cancer and genomic disease treatment. Two types of RNA molecules, i.e. microRNA (miRNA) and small interfering RNA (siRNA), have been extensively used for RNAi. However, numerous issues arise with the delivery of RNAs. Not only can naked RNAs not cross the cellular membrane due to their negative charge, RNAs are also degraded by nucleases and enzymes in plasma, trapped via endosomal uptake, and rapidly eliminated in the renal circulation. A delivery system that evades these mechanisms is needed for effective gene therapy. We have previously developed a novel siRNA-delivery carrier based on tumor-targetable and drug-loadable hyaluronic acid (HA)-nanoparticle (NP) modified with a ZnII-dipicolylamine (DPA/Zn) complex that can selectively bind with phosphate-containing molecules including siRNA. It was demonstrated that DPA/Zn-modified HA-NP (HA-DPA/Zn-NP) can accommodate both hydrophobic small molecule drugs and RNA-based therapeutics in/on the nanoparticle system. In this study, we further optimized the RNAs/drug-loaded HA-DPA/Zn-NPs by introducing a calcium phosphate-based layer onto the NPs to further stabilize the nanoparticle. Drug/gene-loading efficiency was studied and transfection efficiency of RNAs and chemotherapeutics was evaluated in a DU145 prostate cancer cell line. The resulting HCp-NP was found to be an effective delivery system for RNAs and a range of hydrophobic chemotherapeutics.

**Research Category:** Nano Materials

**M. Jane Brennan**

**Institution:** Purdue University

**Title:** Adhesive elastin-based proteins as soft tissue glues

**Authors:** M. Jane Brennan, Jessica Roman, Haefa Mansour, Julie N. Renner, Teresa Lin, Renay S.-C. Su, Jonathan J. Wilker, Julie C. Liu

Surgical adhesives are a promising alternative to sutures. To be a successful surgical adhesive, a product must: be biocompatible, set in a wet environment, and have sufficient adhesive and cohesive properties. In addition, a soft tissue surgical adhesive must also be flexible to prevent excessive stress on surrounding tissue. Unfortunately, most modern adhesives lack at least one of these characteristics. The goal of this project is to utilize protein engineering to develop and characterize a biomimetic soft tissue surgical adhesive. The protein contains two domains: a structural domain that provides flexibility and an adhesive domain that provides the ability to adhere in wet environments. The structural domain is inspired by elastin, a protein that provides elastic properties to tissues such as skin and blood vessels. The adhesive domain is inspired by mussel adhesive proteins (MAPs) which can adhere underwater to nearly any material due to the presence of 3,4-dihydroxyphenylalanine (DOPA). Together, the elastin-based domain and the mussel-inspired domain are engineered to provide the characteristics necessary for an effective surgical adhesive. A protein containing both elastin-like and adhesive domains was expressed in *E. coli* and purified. Following enzymatic conversion of tyrosine to form adhesive DOPA residues, the protein adsorbed to glass more strongly than either BSA or the unconverted protein did. In addition, fibroblasts cultured on the protein showed >98% viability after 2 days, which indicates that the proteins are cytocompatible. Lap shear testing is currently being performed to assess the protein's bulk adhesive properties.

**Young Jo Kim****Institution:** Carnegie Mellon University**Title:** Biologically-Derived Melanin Electrodes in Aqueous Sodium-Ion Energy Storage Devices**Authors:** Young Jo Kim, Wei Wu, Jay F. Whitacre, Christopher J. Bettinger

Biodegradable electronics devices represent an attractive and emerging paradigm as temporary medical devices by addressing the major challenges of (1) supplying sufficient power and (2) reducing the invasiveness of device deployment. Although the high performance energy storages offer a feasible solution, toxic electrodes and electrolytes may cause secondary challenges in adopting biodegradable electronics devices due to their poor biocompatibility. Thus, long-term goal for the biodegradable electronics would provide a biocompatible electronics system that is derived from naturally-occurring and biologically-derived materials. Aqueous sodium-ion charge storage devices combined with biocompatible electrodes are ideal components to power next generation biodegradable electronics. Here we report the use of biologically-derived organic electrodes that are composed of melanin pigments for use in biocompatible energy storage devices. Natural melanin from *Sepia Officinalis* and synthetic melanin are evaluated as anode materials in aqueous sodium-ion storage devices. Na<sup>+</sup>-loaded melanin anodes exhibit the maximum specific capacities of  $30.4 \pm 1.6$  mAhg<sup>-1</sup>. Full cell composed of melanin anodes and  $\lambda$ -MnO<sub>2</sub> cathodes exhibit an initial potential of about 1.0 V with a maximum specific capacity of  $16.1 \pm 0.8$  mAhg<sup>-1</sup>. Natural melanin anodes exhibit higher specific capacities compared to synthetic ones due to the combination of beneficial chemical moieties and physical properties. Taken together, melanin can serve as promising biologically-derived energy storages for powering the edible electronics devices.

**Research Category:** Surface Characterization and Modification

**Paul Chariou**

**Institution:** Case Western Reserve University

**Title:** Engineering Potato Virus X for targeted cancer therapy

**Authors:** Paul Chariou, Karin L. Lee, Dr. Nicole F. Steinmetz

Triple negative breast cancer (TNBC) represents 20% of all breast cancer cases diagnosed and is characterized by the absence of progesterone, estrogen, and HER2 receptors. TNBC is highly metastatic and has limited treatment options, resulting in poor prognosis. 57% of TNBC tumors overexpress the epidermal growth factor receptor (EGFR). This opens the door for the development of targeted therapies. Our work focuses on the development of drug delivery systems targeted towards EGFR+ TNBC using plant viruses. Plant viruses have highly symmetrical nanostructures, are amenable to chemical and genetic engineering, can be produced in high yields, and are biocompatible, biodegradable, and noninfectious in mammals. Plant viruses do not infect, but do enter mammalian cells, therefore providing a unique platform for drug delivery applications. Here we focus on the application of potato virus X (PVX), a flexible rod-shaped virus measuring 515 x 13 nm and consisting of 1270 identical coat proteins. PVX is engineered to display multiple copies of GE11, an EGFR-specific targeting peptide, and RGD, an integrin  $\alpha\beta3$  and  $\alpha\beta5$ -specific targeting peptide. In addition, a cleavable shielding strategy is introduced making use of matrix metalloproteinase (MMP)-cleavable polyethylene glycol (cPEG) chains. PEG chains protect the viral drug delivery system in circulation to increase pharmacokinetics and immune evasion; within the tumor microenvironment MMP-2 and MMP-9 will remove the cleavable PEG shield allowing for cell specific targeting. Flow cytometry and confocal studies indicate that ligand-modified PVX nanoparticles are specifically targeted to TNBC cells. In ongoing studies, the cleavable shielding strategy is evaluated.

## **Hangyu Zhang**

**Institution:** Purdue University

**Title:** Functionalized Graphene Oxide for the Fabrication of Biosensors and Affinity Grids

**Authors:** Hangyu Zhang, Fei Guo, Zhe-fei Li, Alexandra Snyder, Jian Xie, Wen Jiang, and Lia A Stanciu

Here we report a versatile strategy to develop functionalized graphene oxide (FGO) nanomaterials with abundant affinity groups that can capture His-tagged biological particles for the fabrication of biosensors and affinity grids. Initially, the exfoliated graphene oxide (GO) was functionalized by diazonium reaction to introduce abundant carboxyl groups. Then  $\text{Na}_3\text{NTA}$ -Bis(carboxymethyl)-L-lysine hydrate (NTA-NH<sub>2</sub>) and Ni<sup>2+</sup> were connected onto the GO based materials step by step. The functionalization was supported by various characterization techniques. First, the FGO was used to immobilize acetylcholinesterase (AChE) for the construction of pesticide biosensors. Improved electrocatalytic activity, enzyme loading and sensitivity was observed for the FGO covered electrodes. The electrodes also displayed a wide linear response range spanning the substrate concentration from 10  $\mu\text{M}$  to 1mM with an detection limit of 3  $\mu\text{M}$  based on an S/N=3. The stable chelation between Ni-NTA and His-tagged AChE endowed our electrodes with great short-term and long-term stability. Besides, a linear correlation was found between paraoxon concentration and the inhibition response of the electrodes with a detection limit of  $6.5 \times 10^{-10}$  M. Then, we established a simple approach to fabricate affinity grids with FGO for cryo-electron microscopy (cryo-EM) research. His-tagged bacteriophage T7, as a test biological specimen, was captured, and actually purified directly from cell lysates using the affinity grids simultaneously available for single particle cryo-EM. The 3-D reconstruction of T7 indicated that the affinity binding onto the FGO affinity grids did not cause conformational alteration. This strategy provides a platform to fabricate GO based nanomaterials for versatile biomedical applications.

**Kelsey A. Potter****Institution:** Case Western Reserve University**Title:** Characterization and Deployment of Engineered Systems Capable of Reducing Oxidative Stress Surrounding Intracortical Microelectrodes**Authors:** Kelsey A. Potter, Jessica K. Nguyen, Kyle Kovach, John L. Skousen, Jeffrey R. Capadona

Intracortical microelectrodes are capable of recording neuronal signals for use in various rehabilitation applications. Unfortunately, longevity of high quality recorded signals is limited over time. One key hypothesis for loss in device function is the formation of a neurotoxic inflammatory response that forms around the implanted device. Therefore, several research groups have begun to identify and target key mechanistic pathways that may contribute to the neuroinflammatory response. Recently, we demonstrated a prominent role of oxidative stress in mediating neurodegeneration to implanted microelectrodes. Further, we found that short-term systemic administration of an anti-oxidant prevented neurodegeneration at the device-tissue interface up to four weeks after implantation. Where, in our model, improvements in neuronal health were correlated with increased expression of anti-oxidative enzymes around the implanted device. Unfortunately, however, systemic administration of the anti-oxidant also delayed wound healing, as measured by a stab wound control. Therefore, building upon our results, our current work seeks to develop engineered systems capable of providing short-term localized anti-oxidative therapies around intracortical microelectrodes. Here, we will present results from a system which employed direct conjugation of anti-oxidative enzyme mimetics to the surface of implanted microelectrodes. Notably, we found that our modified surfaces were capable of direct reactive oxygen species (ROS) breakdown. Further, our data supports the hypothesis that short-term attenuation of ROS accumulation can result in alterations in inflammatory cell properties in addition to prolonged neuroprotection. Based on our results, future work will investigate how the use of our developed systems will affect neuronal recordings from implanted devices.

**Madhumitha Ravikumar****Institution:** Case Western Reserve University**Title:** Molecular Mediators of Neurodegeneration Surrounding Intracortical Microelectrodes**Authors:** Madhumitha Ravikumar, Smrithi Sunil, William Tomaszewski, Daniel Hageman, Alan Burke, Jeffrey Capadona

Recorded action potentials from small populations of neurons using intracortical microelectrodes have been shown to be a promising source of control signals for various rehabilitation applications. A major hurdle to the use of microelectrode technologies is our inability to consistently record high quality neural signals over time. Increasing evidence suggests that activated microglia and macrophages may serve as the key cellular mediator of the brain tissue response that limits recording quality. Here, we report on the role of a specific microglia co-receptor that is a major component of the innate immune system, cluster of differentiation 14 (CD14). CD14 knock-out (CD14KO) and wildtype mice were implanted with non-functional silicon microelectrodes for 2, or 8 weeks. An additional cohort of wildtype mice was treated with IAXO, a synthetic inhibitor of CD14, in order to investigate the role of IAXO as a potential therapeutic. At two weeks, CD14KO and IAXO treated mice showed significantly improved neuronal survival compared to wildtype mice. Additionally, compared to wildtype controls, CD14KO and IAXO treated mice showed decreased neuroinflammation as indicated by lower amounts of microglia/macrophage activation, a reduced, more diffused astrocytic scar, and reduced blood brain barrier (BBB) disruption surrounding the electrode. At eight weeks, CD14KO mice continued to show significantly higher neuronal survival surrounding the electrode compared to wildtype mice. Our results suggest that CD14 is critical in mediating neurodegeneration to implanted intracortical microelectrodes. These results also suggest the potential of IAXO as a therapeutic target for attenuation of neuroinflammatory events after microelectrode implantation.



**Kyle Kovach****Institution:** Louis Stokes Cleveland VA Medical Center**Title:** The Effects of PEG-Based Surface Modification of PDMS Microchannels on Long-Term Hemocompatibility**Authors:** Kyle Kovach, Jeffery Capadona, Anirban Sen Gupta, Joseph Potkay

The work demonstrates a surface modification for poly(dimethylsiloxane) (PDMS) microfluidic networks that displays a long shelf life as well as extended hemocompatibility. Uncoated PDMS microchannel networks rapidly adsorb high levels of fibrinogen in blood contacting applications. Fibrinogen adsorption initiates platelet activation and causes a rapid increase in pressure across microchannel networks, rendering them useless for long term applications. Here, we describe the modification of sealed PDMS microchannels using an oxygen plasma pre-treatment and poly(ethylene glycol) grafting approach. We present results regarding the testing of the coated microchannels after extended periods of aging and blood exposure. Our PEG-grafted channels showed significantly reduced fibrinogen adsorption and platelet adhesion up to 28 days after application, highlighting the stability and functionality of the coating over time. Our coated microchannel networks also displayed a significant reduction in the coagulation response under whole blood flow. Further, pressure across coated microchannel networks took over 16 times longer to double than the uncoated controls. Collectively, our data implies the potential for a coating platform for microfluidic devices in many blood-contacting applications.

**Research Category:** Tissue Engineering

**Han Shih**

**Institution:** Purdue University

**Title:** Cytocompatible and multi-structural thiol-ene hydrogels formed by visible light-mediated photo-click reactions

**Authors:** Han Shih, Andrew K. Fraser, Chien-Chi Lin

Hydrogels prepared from photopolymerization is an attractive technique for 3D cell studies. Generally, photopolymerizations can be initiated by either ultraviolet (UV) light using a type I initiator (e.g., Irgacure 2959 or lithium arylphosphinate) or visible light with a type II initiator (e.g., eosin-Y) with appropriate co-initiator/co-monomer. Compared to UV light, visible light-mediated gelation is more attractive due to concerns of UV-induced damage. Unfortunately, the utility of visible light-mediated polymerization is greatly limited with the conventional chain-growth photopolymerization which requires the addition of potentially cytotoxic co-initiating components. Here, we report a visible light-mediated step-growth gelation scheme for preparing cytocompatible thiol-ene photo-click hydrogels using photoinitiator eosin-Y without adding any cytotoxic components to achieve rapid gelation. This radical-mediated gelation scheme utilizes norbornene functionalized multi-arm poly(ethylene glycol) (PEGNB) as the macromer and di-thiol containing molecules as the crosslinkers to form chemically crosslinked hydrogels. In addition to investigating the gelation kinetics of the thiol-ene hydrogels, we also used these cytocompatible hydrogels for encapsulating human mesenchymal stem cells (hMSCs) and pancreatic MIN6 cells. Furthermore, the re-excitability of eosin-Y simplifies the process of forming multilayer hydrogels via eosin-Y diffusion and an interfacial polymerization. In sum, this gelation scheme represents a significant improvement over existing visible light-mediated gelation systems and should be of great interest to the field of biomaterials and regenerative medicine.

**David Antonio Cantu****Institution:** University of Wisconsin-Madison**Title:** Bilateral regulation of human monocyte and matrix-encapsulated mesenchymal stromal/stem cell in vitro and in full-thickness cutaneous wounds.**Authors:** David Antonio Cantu, Kedi Xu, Yao Fu, Jaehyup Kim, Xiaoxiang Zheng, Peiman Hematti, Weiyuan John Kao

Mesenchymal stromal/stem cells influence wound healing by secreting immunomodulatory cytokines, growth factors, anti-fibrotic proteins, or directly differentiating into specific tissues. MSCs have previously been administered to promote cutaneous wound healing; however, MSC-based therapies are limited due to poor spatial localization and retention of cell viability and function. Gelatin/poly(ethylene) glycol hydrogels were formed via Michael-type addition for rapid encapsulation of MSCs. Entrapped MSCs retained their multidifferentiation potential within the gelatin/poly(ethylene) glycol biomatrices as assessed by Oil Red-O (adipocyte differentiation), Safranin-O (chondrocyte differentiation), and Alzirin Red S (osteoblast differentiation) staining after 14 days of culture. Gelatin/poly(ethylene) glycol encapsulated MSCs also modulated the pro-inflammatory function of biomaterial-adherent monocytes by attenuating tumor necrosis factor- $\alpha$  secretion at 4 days. MSC-gelatin/poly(ethylene) glycol biomatrices directly applied as dressings to full-thickness wounds in Sprague-Dawley rats demonstrated accelerated wound closure and reepithelialization at 7 days as compared to gelatin/poly(ethylene) glycol hydrogel and control (wounded, no dressing) cohorts. CD68+ macrophage cell density was elevated for the MSC-gelatin/poly(ethylene) glycol biomatrix and gelatin/poly(ethylene) glycol hydrogel cohorts at 4 days and positively correlated with a more favorable wound outcome at 7 days. The MSC-gelatin/poly(ethylene) glycol treatment cohort also displayed attenuated immune cell infiltration, lack of foreign body giant cells, and evidence of neovascularization and granulation tissue that are indicative of favorable wound progression. MSCs retained within the gelatin/poly(ethylene) glycol biomatrix allowed for continued cell presentation adjacent to the wound bed that contributed to early resolution of macrophage-mediated inflammatory events and facilitated proliferation (fibroblast and keratinocyte infiltration) for accelerated wound healing.

**Derek Jones**

**Institution:** Case Western Reserve University

**Title:** Multi-arm PEG hydrogels support enzyme mediated degradation and endothelial cell proliferation

**Authors:** Derek Jones, Junmin Zhu, Roger Marchant

This study investigates the incorporation of bioactivity into poly(ethylene glycol) (PEG) hydrogels in order to control the physical properties of the polymer network and eliminate the need for UV-mediated photopolymerization. Hydrogel networks were polymerized using Michael addition with 4-arm PEG acrylate and thiol containing collagenase sensitive peptide (CSP) as well as the collagenase sensitive and cell adhesive bifunctional peptide (RGD-CSP). The reaction efficiency of the Michael addition reaction was determined and the hydrogels synthesized using this chemistry were characterized for swelling ratio and degradation profile. Cell attachment and proliferation on bioactive hydrogels were also compared for varying peptide ratios. The efficiency of the Michael-type addition reaction was 98% and 100% for the RGD-CSP and CSP peptides respectively. There was no statistical significant effect on the presence of the RGD-CSP bifunctional peptide on the swelling ratio of the hydrogels. CSP-PEG hydrogels incubated in a 0-1 ug/mL range of collagenase solution demonstrated a rate of degradation that was inversely correlated to the concentration of the collagenase in solution. Analysis of the cell attachment and proliferation showed a positive correlation between cell population and ratio of RGD-CSP to total peptide.

**Christopher Mosher**

**Institution:** Cornell University

**Title:** Transformed Aortic Valve Endothelial Cells are Mechanically Active in Disease-Like Conditions

**Authors:** Christopher Mosher, Emily Farrar, Jonathan Butcher

Calcific Aortic Valve Disease (CAVD) starts early in development and encompasses slight calcification of the aortic valve leaflets to complete blockage of outflow from the left ventricle. However, the mechanisms behind CAVD's origin and progression are unknown. This limitation prevents treatment of CAVD early on, and currently the only option for repair is open heart surgery to replace the stenotic aortic valve. We propose that the endothelial to mesenchymal transition (EMT) may contribute the CAVD. As valvular endothelial cells (VECs) break away from the epithelial sheath and enter the interstitial space, their protective barrier is lost. These VECs transition through the EMT into an interstitial-like phenotype and may contribute to the onset of CAVD. Here, VECs are forced through the EMT via NFκB (RelA subunit) transfection. Transfected VECs are studied in several genetic environments to determine the composition of factors influencing the EMT. Findings from these studies suggest that EMT-VECs gain a contractile phenotype after leaving the endothelial lining and entering the interstitium. This is significant, because contractive EMT-VECs may be contributing to the initiation and/or development of CAVD.

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## **POSTER ABSTRACTS**

**Research Category:** Drug Delivery

**Rebecca Scott**

**Institution:** Purdue University

**Title:** Characterization and Delivery of Localized Antithrombotics for the Treatment of Restenosis

**Authors:** Rebecca Scott, Alyssa Panitch

While the number of percutaneous coronary interventions (PCI) performed in the United States has increased by 33%, thrombosis, neointimal hyperplasia, and restenosis remain complications of this procedure and inhibit complete functional recovery of the vessel wall. While some progress has been made via the local delivery of anti-restenotic therapeutics from drug-eluting balloons and stents, the onset of thrombosis has left room for therapeutic improvement. Towards this effort, our laboratory has developed an antithrombotic therapeutic (DS-SILY) consisting of a dermatan sulfate (DS) backbone functionalized with collagen-binding peptides (RRANAALKAGELYKSILYGC; noted as SILY), which effectively inhibits collagen-induced platelet activation and encourages endothelial cell proliferation. Due to the negative charge associated with DS, DS-SILY binds to platelet derived growth factor and interferon- $\gamma$ , in addition to other signaling molecules involved in the restenotic pathway, with high affinity. As such, growth factor-stimulated SMC cultures treated with DS-SILY demonstrate significantly decreased proliferation, migration, and expression of inflammatory cytokines compared to controls. Furthermore, biologically active DS-SILY can be released from water-soluble polymer films developed within our laboratory. These results indicate that the use of DS-SILY as an antithrombotic therapeutic during PCI could aid in the functional healing of the injured vessel wall.

**Edgardo Rivera****Institution:** Case Western Reserve University**Title:** Local delivery of Silibinin from beta-cyclodextrin polymers for the treatment of solid tumors**Author:** Edgardo Rivera, Horst von Recum

The aim of this project is to disrupt the vascular supply of tumors by means of long-term delivery of implantable anti-angiogenic polymers. Long term release may disrupt vasculature by different endothelial cell process such as cell activation, proliferation, migration and tubular morphogenesis. We have developed an implantable polymeric platform and validated its release kinetics with different anti-angiogenic drugs. 5 different anti-angiogenic drugs (Silibinin, Tranilast, SU5416, 2-methoxyestradiol) were loaded into cyclodextrin based polymers in the range of 2.5% to 10% weight of drug/weight of polymer. Drug release was followed by absorbance of aliquots from an infinite sink solution consisting of .25% Tween 80 in saline solution. Bioactive confirmation of drug release was measured by means of scratch wound assay, a proliferation assay and zymographic analysis on different endothelial cell lines. Affinity of drugs towards the cyclodextrin pocket is determined by means of surface plasmon resonance. Of the 4 anti-angiogenic drugs tested 3 showed significant delay in their release as measured by their drug release profiles in vitro. One of the release profiles together with its bioactive proliferation inhibition assay is shown as a representative sample. Bioactivity testing of the dose response shows a dose response of endothelial cells in both proliferation and migration in the range of 50uM to 200uM of silibinin. The anti-angiogenic candidate silibinin showed sustained drug release indicative of an affinity interaction between the drug and the cyclodextrin. Bioactive release tested was demonstrated to be consistently below effective concentrations in vitro.



**Huiying Jia****Institution:** Miami University**Title:** Sustained Ibuprofen Release Using Composite Poly(Lactic-co- Glycolic Acid)/Titanium Dioxide Nanotubes from Ti Implant Surface**Authors:** Huiying Jia, Lei Kerr

Developing coatings on implant surface as drug carriers can reduce organ toxicity and effectively deliver drugs locally to the target compared to the oral approach. Titanium dioxide (TiO<sub>2</sub>) nanotube has great potential for this application for widely used Ti implants due to its high surface area, ability to promote bone growth and biocompatibility. However, there are two issues needed to be solved before further advancing TiO<sub>2</sub> nanotubes technology as drug carriers: uncontrolled drug release and poor mechanical properties. In this study, a drug carrier using a composite of biodegradable polymer/TiO<sub>2</sub> nanotubes is engineered. Ibuprofen is selected as concept drug since it is a commonly used anti-inflammatory, fever and pain reducing drug. In addition, ibuprofen has a very short plasma half-life of only 1~3 hours. A simple characterization method is developed to investigate the infiltration of polymer into TiO<sub>2</sub> nanotubes. Good infiltration was observed of polymer into TiO<sub>2</sub> nanotubes. The synthesized drug carrier demonstrated much better sustained drug release profiles for ibuprofen of 5 days (low molecular weight polymer) and 9 days (high molecular weight polymer) compared to 30 minutes of pure TiO<sub>2</sub> nanotubes. This drug carrier also exhibits much improved mechanical strength and flexibility compared to pure TiO<sub>2</sub> nanotubes.

**Haoyan Zhou****Institution:** Case Western Reserve University**Title:** Non-invasive characterization of polymer degradation using ultrasound elastography (UE)**Authors:** Haoyan Zhou, Monika Goss, Anna Gawlik, Agata Exner

The rational design of polymer drug delivery devices or tissue-engineering constructs would greatly benefit from the ability to monitor polymer material degradation directly at the implantation site. Currently, a number of techniques are available to monitor polymer degradation: as among them gel permeation chromatography (GPC), end group analysis and light scattering, but none of these methods can be used to monitor this process noninvasively. Ultrasound elastography (UE) is a dynamic technique that uses ultrasound to noninvasively assess the mechanical stiffness of materials by measuring materials distortion or strain in response to external compression. In this study, a clinical ultrasound system with spatial resolution 200  $\mu\text{m}$  (axial) and 500  $\mu\text{m}$  (lateral) was used to characterize poly(lactic-co-glycolic acid) (PLGA) in situ forming implant degradation behavior in vitro. Polymer implants were injected into polyacrylamide tissue mimicking phantoms and were scanned daily using our UE technique for up to 30 days. Individual implants were then removed from the phantoms at varying intervals for degradation analysis. By comparing the UE strain results and PLGA degradation profile, a linear correlation was observed between  $1/\text{strain}$  and implants degradation, with polymer stiffness decreasing as a function of increasing degradation. In summary, the presented data indicate that UE may be used as a non-invasive technique to characterize polymer degradation.

**Jialu Yan****Institution:** The University of Akron**Title:** Enzymatic Polyesterification to Produce Functionalized PLA and Poly(n-hydroxyalkanoic acid)s**Authors:** Jialu Yan, Dr. Coleen Pugh

Poly(lactic acid) (PLA) is a biodegradable and biocompatible polyester that has been widely employed in biomedical applications. Our research group has prepared halogenated PLA and poly(lactic acid-co-glycolic acid) (PLGA) using traditional acid-catalyzed polyesterification conditions. Although the chemical synthesis is very efficient, it often leaves chemical residues that have health and safety concerns, which make the product harmful when employed in drug delivery application. This research initially focused on the study of enzymatic copolymerization of LA with 2-bromo-3-hydroxypropanoic acid (BrA) using Novozym 435 (immobilized CALB), which is considered an effective lipase catalyst for polyesterifications. However, the molecular weights of the resulting copolymers are low, which seems to be consistent with other enzymatic polymerizations of short hydroxyalkanoic acids. We are now investigating the effect of the length of the n-hydroxyalkanoic acids on their ability to enzymatically copolymerize with BrA. The molecular weight of enzymatically produced poly(3-hydroxypropionic acid-co-BrA) is similar to that of poly(LA-co-BrA). However, 6-hydroxyhexanoic acid and 12-hydroxydodecanoic acid produce higher molecular weight copolymers with BrA. <sup>1</sup>H NMR spectroscopy also indicate that lactones copolymerize with BrA under enzymatic conditions. This poster will present the synthesis and the results of enzymatic functionalized PLA and linear poly(n-hydroxyalkanoic acid).

**James McMasters****Institution:** Purdue University**Title:** Targeted Thermoresponsive Nanoparticles for Treatment of Atherosclerotic Vascular Disease**Authors:** James McMasters, Nelda Vazquez-Portalatin, Alyssa Panitch

Treatment of atherosclerotic lesions is typically accomplished through percutaneous coronary intervention (PCI), which results in damage to the vessel wall at the site of balloon deployment. This damage exposes the underlying collagenous connective tissue and initiates the coagulation and inflammation cascades leading to thrombosis and restenosis of the treated vessel. The goal of our work is to attenuate this response by simultaneously delivering anti-inflammatory peptides while masking the exposed collagen and promoting endothelial regrowth. To this end we have synthesized a thermosensitive N-isopropylacrylamide (NIPAm) based nanoparticle that contains 5% N,N-methylenebisacrylamide (MBA), 5% 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS), and 1% acrylic acid (AAc), using a free radical precipitation polymerization reaction. To target the nanoparticle system to the exposed collagen, NIPAm nanoparticles were chemically modified to include the collagen binding peptide "GSIT", which was derived from the collagen binding domain of von Willebrand factor. Dynamic light scattering revealed that the modified nanoparticles had temperature dependent hydrodynamic diameters, where the particle size decreased with increased temperature. Additionally, a streptavidin-HRP assay indicated that the peptide was successfully attached to the surface of the nanoparticle and the modified nanoparticles were able to bind to fibrillar collagen at nanoparticle concentrations above 0.1 mg/mL. Future work will focus on characterizing the modified particles' binding under flow conditions, as well as the loading and release of a therapeutic peptide.

**Amy M. Wen****Institution:** Case Western Reserve University**Title:** Enhanced Delivery of PAI-1 Antagonist for Thrombolysis using Elongated Viral Nanoparticles**Authors:** Amy M. Wen, Yunmei Wang, Alice C. Yang, Greg C. Hsu, Huiyun Gao, Daniel I. Simon, Nicole F. Steinmetz

Tissue death and impaired function due to thrombosis is a critical concern in cardiovascular disease. Although fibrinolytic agents used clinically are beneficial for restoring blood flow, their non-specificity can result in adverse complications such as cerebral hemorrhaging. For more controlled delivery to target diseased regions, we turned towards a bio-inspired approach using biomedically relevant plant viral nanoparticles (VNPs) functionalized with a fibrin-specific targeting peptide. VNPs are biodegradable and noninfectious in mammals, and their diversity in shapes and sizes is a unique advantage. Since recent discoveries indicate elongated materials have several advantages over spheres, such as superior margination properties and better evasion of phagocytic clearance, we investigated the enhancement in homing specificity conferred by shape by comparing a rod-shaped vs. a traditional spherical virus with and without a targeting peptide using an in vivo mouse model of thrombosis. Excised arteries were imaged using a Maestro fluorescence imager to determine particle localization. The results indicated that targeted rod-shaped particles show the greatest thrombus targeting, while the non-targeted rods display enhanced homing compared to the spheres. Simultaneously, we are modifying the rod-shaped particles with a PAI-1 inhibitor to help stimulate the endogenous activity of tissue plasminogen activator (tPA) for clot lysis. Assays in vitro demonstrate the efficacy of the PAI-1 antagonist in promoting the activity of tPA. We thus present a new platform for thrombus targeting and are working towards therapeutic formulations that incorporate PAI-1 inhibitors to enhance endogenous fibrinolysis.

**Crystal Shin****Institution:** Purdue University**Title:** Development of in vitro Three-dimensional Tumor Model**Authors:** Crystal Shin, Kinam Park

The in vitro evaluation of chemotherapeutic delivery systems is essential as a prediction of in vivo chemotherapeutic efficacy. Chemotherapeutic agents are typically evaluated by using cellular monolayers cultured in a flat-bottom plastic dish prior to expensive and arduous in vivo studies. Despite its ease of handling, cellular monolayers have provided poorly correlated outcomes of in vivo chemotherapeutic efficacy. In two-dimensional (2D) in vitro environment, morphological differences of the tumor cells and lack of cell-cell and cell-extracellular matrix interactions contribute to the discrepancies in cellular drug responses. Hence, it is important to develop in vitro tumor model which closely mimic the in vivo tumor when studying anti-cancer drug targeting and therapeutic efficacy. The main goal of this study was to develop in vitro three-dimensional (3D) tumor models for evaluation of the efficacy of chemotherapeutic delivery systems. Hydrogel forming biomaterial mimicking the in vivo 3D microenvironment for the tumor cells to proliferate and develop into multicellular tumor spheroids (MTS) was selected. Tumor cells cultured as MTS were used to evaluate chemotherapeutic efficiency of an anticancer drug. In vitro 3D tumor models can bridge the gap between in vitro and in vivo anti-cancer drug evaluations. It is anticipated that success of this research will enhance our understanding of drug delivery mechanisms to develop more efficient drug delivery systems.

**Kihwan Kim****Institution:** Case Western Reserve University**Title:** New in vitro model for testing drug delivery into tumor tissue from capillary vessels in the tumor microenvironment**Authors:** Kihwan Kim, Miklos Gratzl

Drugs are absorbed from blood capillaries by tumor tissue via two routes: extravasation through passive diffusion across the endothelium, and through open leaks of hundreds of nanometers in size that tumor capillaries incorporate. Diffusion of Small drug molecules through vessel walls may become secondary to entering the tissue directly via the leaks. Nanocarriers are thought to leave capillaries exclusively via leaks. This provides better tumor homing properties than classical drug molecules. In vitro studies of drug extravasation and penetration as well as associated local changes in hypoxia and acidity are important in several ways: understanding of interaction between the tumor microenvironment and therapeutics, screening new therapeutics and developing precise tools for optimization of personalized medicine. There are classical in vitro models such as spherical 3D cell construct (Spheroid Model) and other 3D cell cultures to replicate the tumor tissue microenvironment, but they do not incorporate pressure gradient and do not mimic accurately the in vivo geometry, where the tissue surrounds the capillary and not vice versa. Currently we are developing a physical model called "Capillary Model" that replicates the exact in vivo system much better. This presentation describes initial studies on the delivery of Rhodamine B fluorescent dye and the classical small drug molecule doxorubicin in both the spheroid and the capillary model. PC7 breast cancer cells suspended in a hydrogel are used as tissue model. Drug penetration, oxygenation and acidification are measured in depth of the model tissue.

**Research Category:** Materials for Surgical Devices

**Aditya Balasubramanian**

**Institution:** Carnegie Mellon University

**Title:** Rapid stiffness transitioning material designs for biomedical devices

**Authors:** Aditya Balasubramanian, Christopher J Bettinger

Current invasive medical devices such as endoscopes are primarily composed of materials with high elastic modulus ( $E \sim 100$  GPa) such as stainless steel. While this provides rigidity required for certain functionalities, it can potentially lead to tissue damage. For example in lower GI endoscopy, deformation of endoscopes at the corners of the colon wall causes pain and leads to increased chance of tissue damage and perforations. Forces above 54 N on the walls can cause bleeding and perforation leading to emergency medical surgery. To overcome this, device materials must be stiff enough to avoid bucking and carry instruments, while being compliant enough to negotiate tortuosity without tissue damage. One such strategy is to utilize materials with rapid stiffness transition capabilities (from  $E \sim$  GPa to  $E \sim$  MPa). Such materials would enable selective compliance in desired device sections to negotiate tortuosity while retaining stiffness in the rest of the device. Thermoplastics exhibit stiffness modulations along with phase transitions about its glass transition temperature. Rapid stiffness transitions can be achieved by rapid manipulation of bulk temporal profiles of thermoplastics. In order to achieve rapid temporal manipulation, we propose a vascularized thermoplastic material design. Rapid temporal manipulations ( $t \sim$  s) of thermoplastics were achieved by controlling the temperature of liquid perfusate flowed through microfluidic channels embedded in the bulk. This resulted in rapid modulus transitions from  $E' \sim 1$  GPa to  $E' \sim 20$  MPa. Actuation of a macroscopic gripper was demonstrated using this concept of microfabricated rapid stiffness transitioning material design.



**Research Category:** Nano Materials

**Haefa Mansour**

**Institution:** Purdue University

**Title:** Development of Adhesive Elastomeric Proteins for Surgical Adhesive Applications

**Authors:** Haefa Mansour, M. Jane Brennan, Julie C. Liu

This project focused on the development and characterization of a recombinant protein that functions as a surgical adhesive. Surgical adhesives provide a promising alternative to the stiff sutures and staples that often result in external tissue damage when used to close wounds. Ideal surgical adhesives are biocompatible, able to set well and remain sticky in moist conditions, possess strong adhesive and cohesive properties, and exhibit mechanical properties that mimic those of the surrounding tissue. Unfortunately, the commercial adhesives available today are unable to meet all of these criteria. We created a modular protein that combines the adhesive properties of mussel proteins, which are able to strongly adhere to nearly any surface, with the mechanical properties of elastin, a protein that provides flexibility to soft tissues in the body. Thus far, our recombinant protein was successfully cloned into *E. coli* and overexpressed in a 10 L fermentor. The protein was then purified using immobilized metal affinity chromatography, and the pre-adhesive region of the protein was enzymatically converted to impart adhesive properties. We were able to use crosslinking chemistry to form hydrogels from a model protein and show that the gelation time and mechanical properties can be tuned by altering the crosslinker concentration and pH. The mechanical properties of protein hydrogels are being characterized using controlled-force tensile testing. Our preliminary results demonstrate that our model protein has a Young's modulus that is similar to that of soft tissues and may be of interest in surgical applications.

**Meredith Muskovich****Institution:** Carnegie Mellon University**Title:** Hydrogel Templates for Ordered In situ Metallization**Authors:** Meredith Muskovich, Christopher Bettinger

Neural interface applications require bio-electrodes that are mechanically compatible to skin and tissue. Due to mechanical incompatibility, the stiff polymers, silica, and metals used in bio-electrodes contribute to scarring and encapsulation of the tissue surrounding the electrode. Hydrogels have been shown to have mechanical properties similar to that of tissue, allowing them to be excellent materials for bio-devices. It is hypothesized that by utilizing the mechanical properties of hydrogels and the electrical conductive properties of metals, hydrogel matrix based composites with ordered metal microstructures could be utilized as bio-electrodes matching the properties of human tissue. Ortho-Nitrobenzyl methacrylate was incorporated into a hydroxyethylmethacrylate (HEMA) based hydrogel with PEGDMA crosslinking. By varying the percentage of NBMA, the photolabile properties of the hydrogels could be optimized. FTIR and UVVIS were used to observe the single photon UV cleavability, and percentage of incorporation of NBMA of these hydrogels. Mechanical properties of the swollen gels were tested utilizing swelling tests and rheological modulus testing. Amplitude sweeps were used to determine the linear viscoelastic region and the optimized percent strain was taken within this region for frequency sweeps of the hydrogels. Utilizing photolithography techniques, the hydrogels were shown to have selective photolability when masked. Hydrogels with mechanical properties on the order of kPa were synthesized. The exposed areas of the hydrogel formed anionic regions, which were then seeded with cationic silver nitrate. After reduction of the silver cations, it has been shown that ordered metallized structures could be created within the hydrogel matrix.

**Shan Lu**

**Institution:** Cleveland Clinic Foundation

**Title:** Electrospun Spider Silk Fibers Retain the Cyclical Humidity Response Observed in Natural Silk Fibers

**Authors:** Shan Lu, Samuel C. Evans, Ganesh Swaminathan

Major Ampullate (MA) silk is among the most impressive biomaterials due to its unparalleled mechanical properties. However, use of this biomaterial in medical and commercial applications hinges on the ability to artificially produce it while retaining its mechanical properties, which is difficult due to the prohibitive cost of harvesting natural spider silk in bulk and the lack of understanding of how spiders produce solid polymer fibers from an aqueous protein solution. Here, we attempt to reproduce silk fibers from solutions of natural MA silk proteins via electrospinning, and investigate whether these artificial fibers respond to humidity change in a manner similar to natural fibers.

**Jessica Nguyen****Institution:** Case Western Reserve University**Title:** The Neuroinflammatory Response to Mechanically-Adaptive Polymer Implants**Authors:** Jessica Nguyen, Kelsey Potter, Daniel Park, John Skousen, Jeffrey R. Capadona

Neural implants, typically made of metals, silicon, or ceramics, have a much higher mechanical stiffness (~200 GPa) compared to neural tissue (~6 kPa). The mechanical mismatch can result in chronic strain and micromotion between the implant and neural tissue, which may have a significant role in perpetuating the inflammatory response and neurodegeneration at the interface. However, materials that more closely match tissue stiffness are unable to penetrate the brain during initial insertion. To avoid this issue, a bio-inspired, mechanically-adaptive polymer nanocomposite material has been developed based on the dermis of the sea cucumber. These nanocomposite materials have the ability to controllably and selectively switch from a stiff to a compliant state upon implantation. The objective of this study is to examine if compliant nanocomposite implants will be able to attenuate chronic inflammation/neurodegeneration and reduce strain on surrounding tissue. COMSOL modeling of the implants suggest that the nanocomposite significantly reduces strain on surrounding cortical tissue. Additionally, at acute and chronic timepoints after implantation compliant nanocomposite implants exhibit decreased neuroinflammation and neurodegeneration compared to stiff controls. These results demonstrate the contribution of the mechanical properties of the implants on the facilitation of the cortical neural tissue response to implanted devices.

**Jennifer L. Kahn**

**Institution:** Purdue University

**Title:** Collagen matrix templating for increased nano and microstructure of silica thin layers deposited at the cell surface

**Authors:** Jennifer L. Kahn, Rucha Joshi, Sherry Voytik-Harbin, Jenna L. Rickus

Silica is a promising alternative to other current cellular microencapsulation methods for applications including cellular transplants, bacterial biofilm protection, and controlled protein production. The efficacy of silica encapsulation depends on our ability to control pore size distribution, porosity, and chemical stability over time. Current synthetic methods for inducing long-range order in porous silica use high temperatures or harsh solvents, which cannot be used in the presence of cells. Previously, we showed that cell-templated silica sol-gel processing techniques result in a thin (sub-micron) layer of mesoporous silica at the cell surface without cytotoxicity. However, the resulting silica produced using this technique lacks long-range order in the microstructure at the cell surface. Here, we investigate the use of tunable collagen polymers to form a physical and biological template for silica condensation. The collagen polymers allow formation of encapsulation matrix templates that are modulated in terms of their fibril microstructure, physical, and biodegradation properties. We have prepared a series of collagen templates varying in fibril density, interfibrillar branching, and material stiffness. Cell-templated silica deposition conditions were then adapted to the collagen, and collagen matrices were exposed to silica monomers for varying periods of time. Scanning electron microscopy (SEM) and elemental analysis by energy dispersive x-ray spectroscopy (EDX) demonstrate that collagen has the ability to template silica at the level of individual collagen fibrils in a gradient, with higher levels of encapsulation at the surface of the collagen matrix decreasing inward. Silica material properties also were found to be dependent upon collagen matrix properties.

## **Congcong Zhu**

**Institution:** Carnegie Mellon University

**Title:** Light-Induced Remodeling of Physically Crosslinked Hydrogels Using Near-IR Wavelengths

**Authors:** Congcong Zhu, Christopher J. Bettinger

Photodegradable polymers have been studied as light-sensitive biomaterials for various applications including triggerable matrices for controlled drug release, templates for three-dimensional biomolecular patterning and tissue scaffolds. One prevalent strategy to confer photodegradation behavior in hydrogels is to use light-induced uncaging mechanism. Polymeric materials that undergo degradation by single-photon uncaging have limited utility in biomedical applications because UV irradiation can be strongly absorbed by tissue and potentially cause DNA damage in cells. Herein we describe the synthesis and characterization of a class of photolabile hydrogels that can undergo photodegradation upon irradiation with near-IR light which can penetrate deeper into human tissue and present less damage. Linear triblock copolymers composed of poly([methacrylic acid]-co-([6-bromo-7-hydroxycoumarin-4-yl]methyl methacrylate) and poly(ethylene glycol) segments were synthesized using esterification reaction between PMAA-PEG-PMAA and 6-Bromo-4-chloromethyl-7-hydroxycoumarin. Photodegradable physically crosslinked hydrogels have been prepared from self-assembly of amphiphilic triblock copolymers upon introduction into aqueous environment. Hydrogels prepared by phase separation exhibit a dynamic storage modulus of  $139.72 \pm 19.3$  Pa, which shows continuous reduction under UV light exposure as measured by rheometer. Single- and two-photon induced degradation were demonstrated by spatially selective light exposure followed by fluorescent microscopy imaging. Hydrogel disintegration was further investigated by loading secondary reporter dyes into the networks. Reporter molecules are subject to release due to crosslink dissociation upon light exposure. Potential applications of this class of photodegradable hydrogels as remotely cleanable surfaces are also discussed using a model material environment. Taken together, poly(MAA-co-BHCMM)-PEG-poly(MAA-co-BHCMM) physically crosslinked hydrogels exhibit rapid light-induced degradation behavior using light at tissue-transparent wavelengths and could be processed into functional materials for biomedical applications.

**Jordan Boivin****Institution:** Miami University**Title:** Synthesis of Protein-Polymer Hybrid Materials Using Controlled Radical Polymerization**Authors:** Jordan Boivin, Wesley Hall, Dr. Jason Berberich

Controlled radical polymerization has been an effective approach for designing and preparing protein-polymer conjugates. These protein conjugates may be used as primary therapeutic agents, drug delivery devices, biosensors, and catalysts for bioremediation and synthesis of pharmaceuticals. One potential application of a protein-polymer material would be the design of a smart drug delivery device. For example, a glucose responsive polymer utilizing the enzyme glucose oxidase can be designed to release insulin in response to hypoglycemia. Another application would include the design of biocatalysts that improve the solubility and stability of normally insoluble, unstable proteins for synthesis in organic solvents. The method we use, Atom Transfer Radical Polymerization, allows for precise control of the polymer size and low polydispersity, the use of different functional groups, the synthesis of block and gradient polymers, and reaction conditions that are compatible with biological molecules. This method also leaves an initiator site at the end of the polymer chain that can be further modified. Additionally, crosslinking the polymer increases the stability of the protein, prolonging the life of the protein in vivo. For patients, this increases the time between doses. Crosslinking the polymer will also increase stability in organic solvents, aiding in pharmaceutical synthesis. We will discuss our recent work in designing protein-polymer conjugates using Atom Transfer Radical Polymerization technique.

**Stephen Hern**

**Institution:** Case Western Reserve University

**Title:** Shape matters: the diffusion rates of TMV rods and CPMV icosahedrons in a spheroid model of extracellular matrix are distinct

**Authors:** Stephen Hern, Karin L. Lee, Logan Hubbard, Ibrahim Yildiz, Miklos Gratzl, Nicole F. Steinmetz

Cancer therapy drug delivery practices are limited by how poorly drug carriers can typically penetrate tissue. This limitation often causes tumors to receive a non-homogenous distribution of treatment; an issue that contributes to resistance or recurrence of non-treated cancer cells. Contemporary drug delivery vehicles are predominantly spherical in shape. However, recent data suggest that elongated rods and filaments may be better suited for cancer therapy because they have been demonstrated to accumulate more frequently in tumors. In this project, we compare the diffusion rate of icosahedral cowpea mosaic virus (CPMV) versus that of rod-shaped tobacco mosaic virus (TMV) into a spheroid model, a 3D model of the tissue microenvironment that surrounds a capillary. Both viral nanoparticles (VNPs) were labeled on their exterior surfaces with fluorescent dyes. These VNPs were added over agar spheroid model and imaged with a confocal microscope for 6 hours. Each image was analyzed in Matlab to determine the fluorescence intensity of each virus at distances into the spheroid. This analysis indicated that both CPMV and TMV diffused into the spheroid models in a two-phase manner: a fast initial loading phase, followed by a second slower and constant accumulation phase. TMV shows a faster diffusion rate than CPMV in phase I, while phase two shows an opposite trend. This rapid loading of TMV could provide distinct advantages in an in vivo setting by allowing the particles to penetrate into the tissue quickly; which would be expected to increase nanoparticle access while avoiding washout effects.



**Jaqueline Diane Wallat****Institution:** Case Western Reserve University**Title:** The Tobacco Mosaic Virus as a Scaffold for Smart Polymer Nanoparticles**Authors:** Matthew Plecha, Nicole F. Steinmetz, Jonathan K. Pokorski

Viruses are an emerging platform for the synthesis of nanomaterial scaffolds which assemble into homogeneous particles with structures known to atomic resolution. Tobacco-Mosaic Virus (TMV), a rod shaped virus particle (300nm x 18nm) has been used as a platform for smart polymer nanoparticles, is amenable to both interior and exterior surface modifications imparting novel functions into the particle. We report the TMV templated synthesis of polymer composite nanoparticles. Both surfaces of the virus have been modified to incorporate tertiary bromides, followed by polymerization via Atom Transfer Radical Polymerization (ATRP). We demonstrate the utility of these nanoparticles as fluorine MRI agents, an emerging imaging technique for "hot-spot" imaging. Experiments using fluorinating reagents produced the target ATRP monomer, an 8-PEG methyl methacrylate with a trifluoromethoxy-end group, which can be incorporated into protein:polymer hybrid materials for in-vivo hot spot imaging.

**Research Category:** Protein and Cells at Interfaces

**Pitirat Pholpabu**

**Institution:** Carnegie Mellon University

**Title:** Regenerative Integration of Percutaneous Devices Using Macrophage Modulating Elastomers

**Authors:** Pitirat Pholpabu, Christopher A. Bettinger, Phil Campbell

Indwelling lines are used in many common medical interventions including controlled release and support of chronically implanted devices. Over 150 million devices are implanted annually. However, they are also a prominent source of deadly bloodstream infections. The primary mechanism for increased incidence of blood stream infection is incomplete device-skin integration and epidermal downgrowth which eventually leads to device extrusion. Stable regenerative integration of indwelling devices could provide a stable infection barrier. We hypothesize that the regenerative integration can be achieved by increasing regenerative macrophage populations while simultaneously minimizing epidermal downgrowth. Here we present a percutaneous device that (1) promotes the formation of regenerative macrophages through controlled release strategies and (2) reduces epidermal downgrowth via microtopography-modified surfaces. Method: Poly(glycerol sebacate) (PGS) were used as a material for fabricating percutaneous devices to match the skin mechanical properties. Elastomeric controlled release matrices were used to release macrophage phenotypic controlling agents; linoleic acid and pioglitazone. Topographic features were integrated into elastomeric films through replica molding. Biodegradable elastomeric sheets were then fashioned into tubular structures. The extent of tissue-device integration was assessed through histology. Results and Discussions: Crosslinked elastomeric networks permit relatively rapid controlled release of linoleic acid and pioglitazone. The PGS film could be micro-patterned and rolled into a tube. We anticipate that the skin histology will reveal the pro-healing macrophage at the material surface while using the drug-loading tube, and the microtopography will be able to bias the cell migration by reducing epithelial downgrowth.

**Smrithi Sunil****Institution:** Case Western Reserve University**Title:** Characterization of Infiltrating Blood-Derived Cells Surrounding Intracortical Microelectrodes**Authors:** Smrithi Sunil, Madhumitha Ravikumar, Jeffrey Capadona

The stability of the tissue surrounding implanted intracortical microelectrodes is essential in maintaining high quality neuronal signals. Increasing evidence suggests that recording instability may be linked to neuroinflammation. A number of factors including extravasated blood products and macrophage released soluble factors are believed to mediate neuroinflammation and the resulting recording instability. Additionally, recent work has indicated that normal neuronal function may be further impaired by alterations in the local ionic environment due to blood-brain barrier (BBB) dysfunction. Specifically, persistent inflammatory cell trafficking between the brain tissue and the local vasculature may explain observations of chronic BBB dysfunction. However, the biggest limitation in understanding the role of blood-derived cells in neuroinflammation is that there are currently very few widely accepted models to study and/or characterize the BBB. Here, we utilized a bone marrow chimera model to characterize the role of infiltrating blood-derived cells (CFP+ cells) resulting from BBB dysfunction surrounding the electrode up to sixteen weeks post implantation. Infiltrating CFP+ cells were present throughout the brain at initial time points (2 wks) and localized around the electrode at chronic time points (8, 16 wks). Further, co-localization of microglia/macrophages with CFP+ cells indicated the presence of blood-borne macrophages predominantly present around the electrode. Our results suggest that cell trafficking between the native brain tissue and the local vasculature may cause chronic BBB dysfunction, which may adversely affect neuronal health. This model will enable us to better understand the role of cell trafficking and temporal fluctuations in the inflammatory response to microelectrodes.

**John Hermann****Institution:** Case Western Reserve University**Title:** Disruption of Toll-like Receptor Signaling to Improve Tissue Integration of Intracortical Microelectrodes**Authors:** John Hermann, Jessica Nguyen, Madhu Ravikumar, Shruti Sudhakar, Kelly Buchanan

Intracortical microelectrodes have the potential to restore function and sensation to severely paralyzed individuals. Unfortunately intracortical microelectrodes are unable to function reliably long term. Failure is thought to be associated with the tissue response to the implanted microelectrode, especially neuronal loss, blood-brain barrier disruption, and microglial activation. Activation of microglia in response to necrotic cells and infiltrating serum causes the release of pro-inflammatory cytokines and reactive oxygen species, which are harmful to the blood-brain barrier and neurons. Toll-like receptors 2 (TLR2) and 4 (TLR4) on the surface of microglia recognize necrotic cells and infiltrating serum. Therefore, the current study investigated if TLR2 and TLR4 inhibition will attenuate intracortical microelectrode mediated neurodegeneration. TLR2 and TLR4 knockout mice were implanted in the cortex with microelectrodes for 2 or 16 weeks. Analysis of the tissue response to the microelectrode showed decreases in microglial activation, astrocytic scarring, and blood-brain barrier permeability around the electrode site in TLR2 and TLR4 knockout mice relative to wild type mice. Thus, TLR2 and TLR4 are valuable therapeutic targets for improving the tissue integration of intracortical microelectrodes and various implanted central nervous system devices.

**Ruth Herrera-Perez****Institution:** Purdue University**Title:** Scaffold composition alters the morphology and migration characteristics of glioblastoma stem cells in 3D culture**Authors:** Ruth Herrera-Perez, Sherry Voytik-Harbin, Jenna L. Rickus

High invasiveness and recurrence of glioblastoma multiforme (GBM) are linked to a subpopulation of cancer cells with stem cells characteristics that make it the most deadly form of brain cancer. Glioblastoma stem cells (GSC) can fully repopulate a tumor; therefore their targeting is fundamental to efficiently treat the malignancy. GBM is a white-matter disease; but it can also colonize other microenvironments like the basement membrane of blood vessels. To understand the behavior and mechanisms used by GSCs to successfully invade multiple microenvironments, we created a three-dimensional scaffold of collagen-hyaluronan. Our scaffold was investigated along with oligomer type-I collagen, commercial monomeric collagen and Matrigel® as in vitro models to study the morphology, migration and spreading of GSC neurospheres in 3D culture. GSCs show the highest migration and spreading in Matrigel®. The concentration and source of collagen and the presence of HA influence the migration distance. GSCs adopt an elongated morphology in Matrigel® with no separation from the neurosphere contrary to the other matrices where GSC separate easily and mostly exhibit a round-shape with long filipodia. These results suggest that GSCs use diverse cellular mechanisms to invade different ECMs. A deeper knowledge of those differences will help to create multimodal therapies to target all the paths used by GBM to infiltrate healthy tissue.

**William Tomaszewski****Institution:** Case Western Reserve University**Title:** Disruption of Cluster of Differentiation 14 Signaling to Improve Intracortical Microelectrode Integration**Authors:** William Tomaszewski, Madhumitha Ravikumar, Jeffrey Capadona

Advances in microelectrode technologies show promise in several rehabilitation applications. However, our inability to record high quality neuronal signals over time limits the use of these devices long-term. Increasing evidence suggests that activated microglia/macrophages may serve as the key cellular mediator of the brain tissue response that limits recording quality. Specifically, cluster of differentiation 14 (Cd14), is a co-receptor on microglia/macrophages involved in the activation of the innate immune response to implanted microelectrodes. Here, we investigated the contribution of Cd14 from blood derived cells and brain microglia in the propagation of neuroinflammation using a bone marrow chimera model. To investigate the role of Cd14 from infiltrating blood-derived cells versus native brain microglia, Cd14 chimera mice were created, where the Cd14 gene was expressed only in blood-derived cells or brain microglia. IHC analysis for common cellular markers was performed in order to assess the neuroinflammatory response. At two weeks post implantation, Cd14<sup>-/-</sup> mice showed reduced microglia/macrophage activation, astrogliosis, and blood brain barrier disruption compared to wildtype mice. Cd14 chimeras had similar microglia activation and astrogliosis surrounding the electrode when compared to Cd14<sup>-/-</sup> mice. Interestingly, Cd14 chimeras where Cd14 was expressed only in blood-derived cells showed less blood brain barrier disruption and improved neuronal densities compared to Cd14 chimeras where Cd14 was expressed only in the brain. Our results suggest that inhibition of Cd14 specifically from infiltrating blood-derived cells is critical in minimizing neuroinflammation. Our results provide insight into developing more targeted strategies for therapeutic interventions.

**Research Category:** Surface Characterization and Modification

**Lauren Randolph**

**Institution:** Case Western Reserve University

**Title:** Targeting atherosclerotic plaques in vivo using rod-shaped tobacco mosaic virus

**Authors:** Lauren Randolph, Michael A. Bruckman, Emily J. Simpson, Leonard G. Luyt, Nicole F. Steinmentz

The diagnosis and treatment of atherosclerosis often occurs after plaque rupture, resulting in heart attacks and strokes. A diagnostic method that allows for early detection and treatment of atherosclerotic plaques would greatly improve patient outcome. Nanoparticles are well suited for this purpose as they can simultaneously display several different molecule types, such as targeting ligands, stealth coatings, imaging molecules, and therapeutic compounds, providing increased imaging sensitivity and tissue specificity. Viral nanoparticles (VNPs) made in plants are an excellent platform for the development of tissue-specific imaging devices. Naturally occurring, plant VNPs are well characterized with known structures that can be engineered chemically or genetically with atomic resolution, a level of control that cannot yet be achieved using synthetic materials. Tobacco mosaic virus (TMV) is a hollow rod-shaped virus which can be chemically modified with targeting ligands and imaging contrast agents to target receptors present in plaques at early stages of development. Specifically, TMV is modified with fluorophores for optical imaging and a peptide ligand specific for vascular cell adhesion molecule (VCAM-1), receptors present on activated endothelial cells surrounding plaques. Ex-vivo fluorescent imaging of intact aortas indicates that VCAM targeting TMV nanoparticles show increased homing to atherosclerotic plaques in ApoE<sup>-/-</sup> mice compared to the negative controls. Co-localization studies with VCAM receptor, endothelial markers, and macrophages further supported this conclusion. Overall, VCAM targeting TMV particles were found to effectively localize in regions of atherosclerotic plaque buildup, indicating a successful active targeting mechanism.

**Lewis Tian****Institution:** Case Western Reserve University**Title:** Heteromultivalent Ligand Modification to Enhance Specific Bioactivity of Vascular Nanomedicine Platforms**Authors:** Lewis Tian, Christa Modery-Pawlowski, Madhumitha Ravikumar, Timothy Wong, Victor Pan, Michael Dzuricky, Anirban Sen Gupta

Active targeting of nanomedicine vehicles via surface-modification with cell-specific ligands can enhance site-selective delivery of therapeutic cargo. In this context, vehicles for vascular drug delivery have to not only bind to the target site, but also resist dislodgement under blood flow. We postulate that modifying the nanovehicle surface with multiple ligand types (heteromultivalent modification) that simultaneously bind to multiple target epitopes, can enhance the binding specificity, as well as, maintain stable attachment under flow. To this end, platelets provide an excellent biological model, as they render hemostasis by adhering onto vWF via GPIb $\alpha$  and collagen via GPIa/IIa and GPVI, at a vascular injury site, and undergoing subsequent aggregation by binding to fibrinogen via GPIIb-IIIa and to sialoproteins via P-selectin. These same ligand-receptor activities become excessive in vascular diseases like inflammation and thrombosis, and hence mimicking them on a synthetic vehicle can provide effective platforms for vascular drug delivery. Therefore, we have investigated two platelet-mimetic nanomedicine platforms via heteromultivalent modification of liposomes, one mimicking platelet's 'aggregatory' functionalities by simultaneous binding to GPIIb-IIIa and P-selectin, and, the other mimicking platelet's 'adhesive' functionalities by simultaneous binding to vWF and collagen. Using epifluorescence microscopy, we have studied the binding and retention of these vehicles under flow at 0-60 dynes/cm<sup>2</sup> on appropriate target surfaces. Our results showed significantly enhanced binding and stable retention of the vehicles on their respective substrates under low-to-high shear. These platforms can be envisioned to carry various therapeutic and imaging agents selectively to vascular disease sites that exhibit high platelet activity.



**Karin L. Lee**

**Institution:** Case Western Reserve University

**Title:** In vitro and In vivo Evaluation of the Immunogenic Properties of PEGylated Potato Virus X

**Authors:** Karin L. Lee, Sourabh Shukla, Nadia Ayat, Mengzhi Wu, Nicole F. Steinmetz

Each year, approximately 1 million new cases of cancer are diagnosed. Recent work in cancer therapy has focused on the development of nanoparticles to deliver chemotherapeutics to specific tissues and cells. Encapsulation in nanoparticles has been shown to decrease side effects of chemotherapies, as well as increase their overall efficacy. However, nanoparticles suffer from detection and clearance by the immune system, which can be attributed to the non-specific innate immune response as well as adaptive immunity following multiple injections. Our lab focuses on the use of plant viral nanoparticles (VNPs) and drug delivery vehicles. Plant VNPs have symmetrical structures that are amenable to chemical and genetic engineering and can be produced at high yields in plants. In addition, they are biocompatible, biodegradable, and non-infectious in mammals. Potato virus X (PVX) is a flexible rod-shaped virus measuring 515 x 13 nm and consisting of 1270 identical coat proteins, each containing a solvent exposed lysine that can be modified by N-hydroxysuccinimide chemistry. Here, we investigate the immunogenicity and biocompatibility of PVX when modified with various polyethylene glycol (PEG) shields. Specifically, we investigate the effect of molecular weight and conformation of PEG on the in vitro and in vivo properties of PVX-PEG.

**Aaron Kosinski****Institution:** Purdue University**Title:** Characterization of a Dynamic PLGA Core + pNIPAM Shell Nanoparticle System for Targeted Drug Delivery Applications**Authors:** Aaron Kosinski, Jamie Brugnano, Brandon Seal, Frances Knight, Alyssa Panitch

Poly(lactic-co-glycolic acid) (PLGA) is a popular material used to synthesize nanoparticles (NPs) for drug delivery. However, PLGA NPs lack desirable attributes including active targeting abilities, resistance to aggregation during lyophilization, and the ability to respond to dynamic environmental stimuli. To overcome these issues, we synthesized a NP consisting of a static PLGA core encapsulated within a dynamic shell of poly(N-isopropylacrylamide) (pNIPAM). Dynamic light scattering (DLS) and transmission electron microscope (TEM) imaging were used to characterize the NPs. While a collagen type II binding assay showed successful modification of these NPs with an active targeting moiety. In the future, we plan to assess how these core + shell NPs facilitate the delivery of therapeutics in various disease models both in vitro and in vivo.

**James Cole****Institution:** Cleveland State University**Title:** Responsive nanoparticles of elastin like polypeptides for theranostic applications**Authors:** James Cole, Nolan B. Holland

We have designed, synthesized and characterized elastin-like polypeptide (ELP's) nanoparticles for use in theranostic applications. The particles are composed of a negatively charged oligomerization domain, a protein based MRI contrast agent and the C terminal targeting domain of the gastrin release peptide (GRP) fused to ELP's that form the core of the particles. Through the use of molecular biology techniques the constructs containing these components were produced in a "one-pot" manner, with no additional conjugation steps necessary. They were then expressed and purified in *E. coli*. Dynamic light scattering and SEM data confirms the nanoparticle formation as well as the ability of the construct to behave in a responsive manner after crosslinking. Immunohistochemistry experiments were performed to confirm targeting to GRP positive cell lines and magnetic resonance activity was confirmed. Contrast agent characterization was performed and relaxivity values have been confirmed as well as gadolinium binding capabilities.

**Michael McBurney****Institution:** Case Western Reserve University**Title:** Development of a deterministic antibody array display technology using a plant virus-based molecular scaffold**Authors:** Michael McBurney, K.Chen, M.D. Glidden, J. Whitney, D. A. Thompson, P.E. Dawson, and N.F. Steinmetz

The success and utility of antibodies and nanoparticle-antibody conjugates in medical imaging, diagnostics, and therapy has stimulated the need for evermore effective antibody display strategies. Contemporary nanoparticle-antibody conjugates have been synthesized using covalent linkage techniques. However, non-specific conjugation and harsh reaction conditions can damage the antibody, hampering antigen recognition and/or affinity. To address this challenge, we explored a non-covalent display strategy making use of a deterministic 3D molecular scaffold. Specifically, we covalently modified 30 nm diameter cowpea mosaic virus (CPMV) capsids to present Fc-III, an Fc $\gamma$ RI-like peptidomimetic, that binds tightly to the Fc regions of antibodies with varying immunoglobulin subclass and species specificity. Binding affinities of the CPMV-Fc-III complexes to a variety of immunoglobulin subclasses from various host species were obtained using surface plasmon resonance. Surface plasmon resonance measurements yielded strong binding of CPMV-FcIII to human IgG, with preferential binding to human IgG1 and IgG3 and low to moderate binding to human IgG2 and IgG4. Additionally, we observe substantial reactivity with IgG derived from mouse, goat, rabbit, and rat hosts as well as with chicken IgY was also observed. The CPMV-FcIII complex exhibited no measurable affinity to human IgE. CPMV-FcIII was shown to bind with high affinity to both human and murine IgG subclasses, suggesting that it can be used in applications, which may utilize a wide variety of immunoglobulin targeting moieties. Further, this formulation shows promise for applications in targeted drug and contrast agent delivery.

**Luke Klosterman****Institution:** Carnegie Mellon University**Title:** Fabrication of compliant electrode by in situ silver film formation on hydrogel**Authors:** Luke Klosterman, Meredith Muskovich

Silver films have been formed on poly(hydroxyethyl methacrylate-acrylic acid-polyethylene glycol dimethacrylate) and poly(hydroxyethyl methacrylate-nitrobenzyl methacrylate-polyethylene glycol dimethacrylate) hydrogels by reduction in situ of silver nitrate with hydroquinone. The silver preferentially aggregates into bulk structures at the gel-water interface. The amount of resulting silver on the surface depends on the concentration of carboxylic acid groups in the gel. Spatially selective exposure of the NBMA gels to ultraviolet light produces carboxylic acid groups which serve to localize the silver film formation. The silver films are electrically conductive and adherent even after deformation of the gel. The morphology of the silver is controlled by the ionic concentration at the surface of the gel. There is a transition from isolated particles at high ionic strength to 2-dimensional, connected disks at low ionic strength.

**Research Category:** Tissue Engineering

**Charles W. Peak**

**Institution:** Purdue University

**Title:** Degradable Hydrogels from Poly(ethylene glycol)-Poly (L-lactic acid) and Collagen Networks

**Authors:** Charles W. Peak, Saumya Nagar, Ryan D. Watts, Gudrun Schmidt

We present an injectable and degradable PEG/collagen hydrogel system with robust networks for use as elastomeric tissue scaffolds. Poly(ethylene glycol)- Poly (L-lactic acid) was covalently cross-linked and collagen was physically cross-linked to form a semi-interpenetrating hydrogel network. The mechanical strength of the hydrogels depend predominantly on the PEGp11a concentration but the incorporation of collagen into the PEGp11a network enhances hydrogel viscoelasticity, and elongation.. Experimental data show that this hydrogel system exhibits tunable mechanical properties. The results support the prospect of a robust and semi-interpenetrating biomaterial for elastomeric tissue scaffolds applications.

**Fei Lin**

**Institution:** The University of Akron

**Title:** Post-electrospinning “Click” Modification of Degradable Amino Acid-based Poly(ester urea) Nanofibers

**Authors:** Fei Lin, Yujia Yi, Matthew L. Becker

Amino acid-based poly(ester urea)s (PEU) are emerging as a new class of degradable polymers that have shown promise in regenerative medicine applications. Herein, we report the synthesis of PEUs carrying pendent “clickable” groups on modified tyrosine amino acids. The pendent species include alkyne, azide, alkene, tyrosine-phenol, and ketone groups. PEUs with Mw exceeding to 100k Da were obtained via interfacial polycondensation methods and the concentration of pendent groups was varied using a copolymerization strategy. The incorporation of derivatizable functionalities is demonstrated using  $^1\text{H}$  NMR and UV-Vis spectroscopy methods. Electrospinning was used to fabricate PEU nanofibers with a diameters ranging from 350 nm to 500 nm. The nanofiber matrices possess mechanical strengths suitable for tissue engineering (Young’s modulus:  $300\pm 45$  MPa; tensile stress:  $8.5\pm 1.2$  MPa). A series of bioactive peptides and fluorescent molecules were conjugated to the surface of the nanofibers following electrospinning using bio-orthogonal reactions in aqueous media. The ability to derivatize PEUs with biological molecules using translationally relevant chemical methods will significantly expand their use in vitro and in vivo.

## **Yiting Hao**

**Institution:** Indiana University-Purdue University at Indianapolis

**Title:** Visible light cured thiol-vinyl hydrogels with tunable degradation for 3D cell culture

**Authors:** Yiting Hao, Han Shih, Zachary Munoz, Arika D Kemp, Chien-Chi Lin

We report a diverse visible light mediated and highly tunable thiol-vinyl gelation system for fabricating cell-instructive hydrogels. Gelation was achieved via a mixed-mode step-and-chain-growth photopolymerization using functionalized 4-arm poly(ethylene glycol) as backbone macromer, eosin-Y as photoinitiator, N-vinylpyrrolidone (NVP) as co-monomer and di-thiol containing molecule as dual purpose co-initiator/cross-linker. The major differences between current and prior visible light mediated photopolymerization are that: (1) the co-initiator triethanolamine (TEOA) used in the previous systems was replaced with multifunctional thiols and (2) mixed-mode polymerized gels contain less network heterogeneity. The gelation kinetics and gel properties at the same PEG macromer concentration could be tuned by changing the identity of vinyl groups and di-thiol cross-linkers, as well as concentration of cross-linker and NVP. Specifically, acrylate-modified PEG afforded the fastest gelation rate, followed by acrylamide and methacrylate-functionalized PEG. Increasing NVP concentration also accelerated gelation and led to a higher network cross-linking density. Further, increasing di-thiol peptide concentration in the gel formulation increased hydrogel swelling and decreased gel stiffness. Due to the formation of thiol-ether-ester bonds following thiol-acrylate reaction, the gels degraded hydrolytically following a pseudo first order degradation kinetics. Degradation rate was controlled by adjusting thiol or NVP content in the polymer precursor solution. The cytocompatibility and utility of this hydrogel system were evaluated using in situ encapsulation of human mesenchymal stem cells (hMSC). Encapsulated hMSCs remained alive (>90%) throughout the duration of the study and the cells were differentiated down osteogenic lineage with varying degrees by controlling the rate and mode of gel degradation.



## **Yuqian Chen**

**Institution:** Purdue University

**Title:** Determining the Extent of Crosslinking in Resilin-based Hydrogels

**Authors:** Yuqian Chen, Renay S.-C. Su, Julie C. Liu

Recombinant proteins are promising materials for tissue engineering applications. Our lab is currently engineering recombinant proteins based on the resilin protein. Resilin is an elastomeric protein found in insect cuticles. It has high resilience, which means that it can be stretched as well as compressed repeatedly without permanent deformation. Materials with high resilience may be attractive candidates to serve as cartilage scaffolds since cartilage undergoes repetitive compression.

Our lab engineered recombinant resilin-based proteins using the resilin sequence derived from mosquito. Lysine residues in the protein sequence serve as crosslinking sites. The mechanical properties of resilin-based proteins can be tuned by changing the extent of crosslinking. The crosslinking degree can be measured by a colorimetric assay that uses 2,4,6-trinitrobenzene sulfonic acid (TNBSA). When TNBSA reacts with primary amines, it turns orange, and the degree of color change can be measured at 355nm. Our results show that the crosslinking degree depends on two factors, protein concentration and the ratio between crosslinking sites and crosslinker.

**Nida Tanataweethum**

**Institution:** Indiana University-Purdue University Indianapolis

**Title:** Mechanical Property and Biocompatibility of PLLA/ DCPD Composite 3D Scaffolds

**Authors:** Nida Tanataweethum, Tien-Min G. Chu, Wai Ching Liu

Introductions: Dicalcium phosphate dihydrate (DCPD) cements have been used for bone repair due to its excellent biocompatibility and resorbability. However, DCPD cements are typically brittle. To address these limitations, the addition of sodium citrate as a regulator and poly-L-lactic acid (PLLA) as reinforcing agent were proposed in this study. Objectives: 1) To develop composite PLLA/ DCPD scaffolds to improve the toughness. 2) To examine the biocompatibility of these scaffolds. 3) To investigate their degradation behaviors. Materials and Methods: DCPD cements were synthesized with a 1:1 molar ratio of monocalcium phosphate monohydrate and  $\beta$ -tricalcium phosphate with deionized water and sodium citrate. The specimens were prepared with powder to liquid mass ratio (P/L) of 1.00, 1.25 and 1.50. The composites were fabricated by coating DCPD specimens with 5 % PLLA. The mechanical properties of specimens before and after the in-vitro degradation (day 1, week 1, 2, 4, 6, and 8) were measured with diametral tensile strength and fracture energy. In addition, biocompatibility of the scaffolds was investigated with dog bone marrow stromal stem cells (BMSCs). Results: the addition of sodium citrate and PLLA coating significantly improved the mechanical properties of DCPD scaffolds ( $p < 0.05$ ). The range of diametral tensile strength was 0.50-2.70 MPa and the range of fracture energy was 0.80-9.90 N-mm. Moreover, both DCPD and composite were biocompatible with BMSCs

Conclusion: a combination of template casting and polymer coating can be applied to fabricate cement/polymer scaffolds for bone tissue regeneration with excellent mechanical properties and biocompatibility.

**Nelda Vazquez-Portalatin****Institution:** Purdue University**Title:** Synthetic Peptidoglycan Lowers Friction Levels in Articular Cartilage Surface**Authors:** Nelda Vazquez-Portalatin, Alyssa Panitch

Articular cartilage is composed of chondrocytes that produce collagen and proteoglycans to form the extracellular matrix (ECM). Aggrecan (AGG) monomers, the main proteoglycan in cartilage, bind to hyaluronic acid (HA) interweaving themselves in the cartilage ECM and conferring the ECM with high compressive strength and protecting the collagen type II present from degradation. In OA, matrix metalloproteases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) are responsible for the degradation of AGG. Once AGG has been degraded, other ECM components, including collagen type II, are exposed to degradation. Lubricin, a superficial zone glycoprotein, is involved in the boundary lubrication and maintenance of low friction levels as well as the protection of articular cartilage surfaces. Lack of lubricin has been associated with joint debilitation and its restitution has been suggested as a potential treatment of osteoarthritis. Thus, this research studies the effect of a synthetic biomimetic peptidoglycan on the friction levels between AGG-depleted articular cartilage surfaces.

**Lin Lin**

**Institution:** Case Western Reserve University

**Title:** Biomimetic Engineered Poly (ethylene glycol) Hydrogel for Smooth Muscle Cell Migration

**Authors:** Lin Lin, Junmin Zhu, Kandice Kottke-Marchant, Roger E. Marchant

We report on a biomimetic scaffold as a model system to evaluate smooth muscle cell (SMC) migration in three dimensions (3D). To accomplish this, bio-inert poly (ethylene glycol) (PEG) based hydrogels were designed as the scaffold substrate. To mimic properties of the extracellular matrix (ECM), cell adhesive peptide (GRGDSP) derived from fibronectin, and collagenase sensitive peptide (GPQGIAGQ) derived from collagen type I, were incorporated into the PEG macromer chain. Copolymerization of the biomimetic macromers results in the formation of bioactive PEG hydrogels with cell adhesivity and biodegradability. By utilizing these biomimetic scaffolds, we studied the effect of adhesive ligand concentration, proteolysis, and network cross-linking density on cell migration. Our results showed that 3D SMC migration has a biphasic dependence on adhesive ligand density, and both adhesive and collagenase sensitive peptides were required for cell migration to occur. Furthermore, network cross-linking density was shown to dramatically influence the behavior of cell migration in the hydrogels.

**Emma Headley****Institution:** Case Western Reserve University**Title:** Enhanced Osteogenic Differentiation of Adipose-Derived Stem Cells in Growth Factor Presenting Gelatin Hydrogels**Authors:** Julia Samorezov, Emma Headley, Eben Alsberg

Human adipose-derived stem cells (hASCs) show great potential for use in bone tissue engineering. These cells are easily obtained and undergo osteogenic differentiation *in vitro* and *in vivo* in response to bone morphogenetic protein-2 (BMP-2) when cultured on ceramic scaffolds. However, the role of BMP-2 on hASC osteogenesis in hydrogels is unknown. Here, the effect of BMP-2 on hASCs in methacrylated gelatin (gelMA) hydrogels was investigated. To make these hydrogels, passage 3 hASCs obtained from lipoaspirate were added at 10 million cells/mL to GelMA solutions containing photoinitiator. For growth factor loaded hydrogels, 25 or 50  $\mu\text{g}$  BMP-2/mL gelMA was added to the solution. After UV crosslinking, hydrogels were cultured in DMEM-F12 containing 10% serum, ascorbic acid and  $\beta$ -glycerophosphate. At designated time points, hydrogels were evaluated for DNA, expression of alkaline phosphatase (ALP), an early osteogenic marker, and staining for calcium, a late osteogenic marker. A statistically significant, BMP-2 concentration-dependent increase in hASC expression of ALP was found. Notably, this occurred in the absence of dexamethasone, a component of most osteogenic media. Additionally, hydrogels with 50  $\mu\text{g}/\text{mL}$  BMP-2 were the only group to show construct mineralization at 4 weeks, even when compared to hydrogels cultured with exogenous BMP-2. GelMA is a promising biomaterial to deliver BMP-2 to hASCs: it is injectable, achieves the same magnitude effect with much less growth factor than exogenous delivery, and maintains growth factor bioactivity. Future work will include tailoring BMP-2 spatiotemporal presentation and evaluating its effects on cells from multiple donors.

**Nathan Millard****Institution:** Miami University**Title:** Development of a Hydrostatic Pressure Chamber for Determining the Effect of Pressure on Liver Progenitor Cells**Authors:** Nathan Millard, Alyssa Denis, Emily Maggio, Sarah McMullen, Michael Weeks, Jessica L. Sparks

One of the least understood characteristics of hepatic progenitor cell (HPC) biology is the effect of mechanical forces on their growth and differentiation. In vivo, HPCs are exposed to mechanical forces due to hydrostatic pressure in the progenitor cell niche. Similarly, HPCs in bioengineered scaffolds may be exposed to hydrostatic pressure during seeding and perfusion maintenance of bioengineered liver tissue. For these reasons, it is important to understand how mechanical forces such as hydrostatic pressure affect HPC development. To test the effects of pressure on HPC growth and differentiation, controlled hydrostatic pressure must be applied to the cells in culture. The goal of this project was to develop a hydrostatic pressure chamber that can mimic the range of physiological pressures in native liver. The hydrostatic pressure chamber developed in this work successfully generated pressures from 1 to 24 mmHg, spanning the range reported for healthy (0-5 mmHg) and cirrhotic (>19 mmHg) liver. The system features continuous real-time monitoring of system pressure using feedback control. Continuous air circulation permits gas exchange, and a 0.2-micron sterile filter minimizes the contamination risk. The design includes three cell chambers which can be connected and disconnected independently. To mimic in vivo conditions, the cell chambers are positioned inside an incubator at 37 C, and a CO<sub>2</sub> monitoring system maintains the carbon dioxide concentration at 5%. Preliminary testing showed that the hydrostatic pressure chamber design successfully provided constant hydrostatic pressure over a 24 hour period with a precision of approximately  $\pm 1$  mmHg of the target pressure.

**Phuong Dang****Institution:** Case Western Reserve University**Title:** Guiding chondrogenesis and osteogenesis with hydroxyapatite and BMP-2 incorporated within a high-density hMSC system**Authors:** Phuong Dang, Xiaohua Yu, Caitlin Bowerman, Neha Dwivedi, William Murphy, Eben Alsberg

Tissue engineering solutions are necessary to meet the great clinical need for bone and cartilage repair. Multipotent and easily accessible, human bone marrow-derived stem cells (hMSCs) are an attractive cell source. Hydroxyapatite has been widely used for bone TE due to its osteoconductivity and chemical resemblance to bone mineral, and has also been reported to promote cartilage repair in vivo. While BMP-2 is a well-known osteogenic inducer and has been shown to enhance chondrogenesis when combined with TGF- $\beta$ 1 or - $\beta$ 3, it is unclear whether BMP-2 alone can reliably induce cartilage formation by hMSCs. To explore the roles of hydroxyapatite and BMP-2 on chondrogenesis and osteogenesis in high-density hMSC cultures, a system of aggregates incorporated with mineral coated hydroxyapatite microparticles (MCM) capable of controlled, sustained BMP-2 release was developed. Cells-only aggregates treated with exogenous BMP-2 had no GAG but a significant increase in calcium content, indicating that intramembranous ossification may have occurred and confirming the role of BMP-2 as an osteogenic inducer. MCM appears to be a chondrogenic inducer as shown by GAG production, and this effect was accelerated with BMP-2. The presence of MCM and BMP-2 may have promoted endochondral ossification that resulted in cartilage formation occurring prior to enhanced matrix mineralization. The released BMP-2 from incorporated MCM exhibited the same level of bioactivity as exogenous BMP-2 with regard to inducing chondrogenesis, osteogenesis and mineralization. The inclusion of BMP-2-loaded MCHA may overcome the transport limitations and time/cost inefficiencies of exogenous supplementation.









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