ABSTRACTS:

Oral Presentations

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Development and characterization of novel parthenolide delivery system for treatment of acute myelogenous leukemia
Parthenolide (PTL) has proved to be effective at eradicating cancer cells, including leukemia stem cells, but its low solubility in blood limits its use therapeutically. We propose a way to circumvent this problem through the development of a polymeric delivery system. We are utilizing core-shell micelles to enable robust PTL loading within the micelles' hydrophobic interior, and we aim to increase PTL's solubility and circulation time in vivo with a protective hydrophilic corona. Specifically, the micelles are comprised of diblock copolymers containing hydrophilic blocks of poly(styrene-alt-maleic anhydride) (PSMA) and hydrophobic blocks of poly(styrene). These diblock copolymers were synthesized using reversible addition-fragmentation chain transfer (RAFT) polymerization to provide controlled polymer chain growth with polydispersity indices of 1.3 or less. Three polymers with molecular weights ranging from 17 to 47 kDa and estimated hydrophobic:hydrophilic block ratios between 0.6 – 0.8 were synthesized and characterized with respect to micelle size, PTL loading, and leukemia cell cytotoxicity. All three polymers self-assembled into spherical micelles with diameters of approximately 25 nm, and successfully loaded PTL with efficiencies ranging between 20% and 40%. These PTL-loaded micelles produced a 50% reduction in MV4-11 leukemia cell viability at PTL doses of 5 μM. In addition, unloaded micelles at these dosages exhibited no significant cytotoxicity towards these cells.

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Reverting antibiotic tolerance of bacterial persisters by brominated furanones
Bacteria are well known to obtain intrinsic tolerance to antibiotics by forming metabolically inactive cells, known as persister cells. Such intrinsic tolerance presents a great challenge to infection control. Recent evidences suggest that persister formation in Pseudomonas aeruginosa is controlled by cell density through a cell-cell signaling system known as quorum sensing (QS). Thus, new therapies targeting quorum sensing may have potential to effectively control chronic infections by eliminating persister cells. Here we report that several quorum sensing inhibitors, brominated furanones, can revert P. aeruginosa persisters to an antibiotic sensitive state. For example, (E)-4-bromo-5-(bromomethylene)-3-methylfuran-2(5H)-one (BF8) was found to reduce the tolerance of P. aeruginosa PAO1 persister cells to ciprofloxacin by around 1 log compared to furanone free control at growth non-inhibitory concentrations.

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Self assembly of amyloid beta particles over disulfide functionalized nano gold colloidal particles

A key step in fibrillogenesis of amyloid beta protein (Ab) causing Alzheimer's disease is a formation of an oligomer intermediate under a reversible process. While it is challenging to extract this oligomer form, the Ab coated gold nanoparticles were found to prepare this oligomer form with a help of a specific nanosurface potential. In order to further clarify the role of nanoscale surface, the surface of gold colloid was functionalized with a series of dialkoxy disulfides and self-assembly of Ab1-40 peptide was investigated. As pH was externally altered between pH 4 and 10, phenyl-bezyilic dialkoxy disulfide functionalized gold exhibited a quasi reversible color change, implying that it has a great potential of controlling a reversible self-assembly process. However, no reversible colour changes were observed for nitro-, chloro-bezyilic dialkoxy disulfide functionalized gold colloids.

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Effect of peptide headgroups on lipid-mediated nucleic acid delivery and transfection

Gene therapy aims to replace, correct, or knockdown the genes responsible for a variety of diseases. Encouraged by initial success in clinical trials, current biomaterials research is focused on improving gene therapy outcomes by engineering nonviral vectors that enhance biocompatibility, localization, and transfection efficacy. By designing a series of cationic lipids with di- and tripeptide headgroups, we were able to study the effect of headgroup charge and headgroup length on the supramolecular structures formed with DNA or siRNA, as well as the resulting delivery and transfection outcomes. Lipoplex structures formed from DNA and lipopeptides were stable at lower charge ratios and smaller in diameter than their siRNA-lipopeptide counterparts. Interestingly, tripeptide lipids showed better DNA transfection efficiency than the dipeptide lipids, while both di- and tripeptides were equally successful in siRNA-based knockdown experiments. Cellular uptake studies revealed differences in the delivery performance of these lipids, with high rates of DNA and siRNA intracellular delivery only when using the tripeptide lipid. These studies, combined with ongoing in vivo experiments, have expanded our library of lipids for both DNA and siRNA delivery and advanced our understanding of how chemical composition affects the supramolecular structure of lipoplexes and influences transfection efficiency.

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6-Bromoindirubin-3'-Oxime (BIO) promotes proliferation and population homogeneity in mesenchymal stem cells

The process of bone healing is a highly orchestrated process involving mesenchymal progenitor cells. The cascade begins with recruitment and robust proliferation of these cells followed by differentiation to osteogenic and chondrogenic cell types, which produce matrix that eventually becomes mineralized, forming bone through highly regulated processes. Thus, promoting proliferation of mesenchymal progenitors is a key step in

recapitulating the healing process in a variety of bone defects (allografts, fractures, etc.). However to date, controlled, robust proliferation of stem cells in vivo has been a major challenge.

In this work, we treated mesenchymal stem cells (MSCs) in vitro with the soluble small molecule GSK3β (glycogen synthase kinase 3β) inhibitor, 6-bromoindirubin-3'-oxime (BIO). BIO, a known Wnt/β-Catenin agonist, was found, in a dose-dependent manner, to promote robust MSC proliferation and undifferentiated stem cell marker expression (Nanog, Oct4, and Sox2). To exploit BIO's effects in the context of fracture healing, we are currently developing degradable hydrogels that permit BIO-mediated proliferation while serving as a temporary MSC delivery platform for use in vivo.

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Polysialic acid based nanoparticle drug delivery system
Polysialic acid (PSA) is a rarely investigated polysaccharide which is non-immunogenic, biodegradable, very hydrophilic, and has no known receptor in human body. With this favorable properties, PSA has potential to prolong the circulation time of therapeutics and improve therapeutics efficacy in human body with no side effect. In this study, we developed two PSA based nano-sized drug carrier systems for disease modifying anti-rheumatic drugs (DMARDs)-cyclosporine and methotrexate, which both have severe side effects. PSA was modified with long hydrophobic chain-polycaprolactone (PCL). This system can self-assemble to form micelle that was able to encapsulate hydrophobic cyclosporine. For the other system, we complicated positively charged trimethyl chitosan (TMC) with PSA which is naturally negatively charged. This system can entrap methotrexate efficiently. Both system demonstrate improvement of drug stability and a favorable size for passive targeting for inflammable tissue.

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Modification of poly(HEMA) with reversibly associating side-groups
Poly(hydroxyethyl methacrylate) (polyHEMA) is an important and versatile biomaterial well known for its role in soft contact lenses. We are exploring the use of reversibly associating groups to tune polyHEMA's mechanical properties and water swelling behavior. A series of linear poly(HEMA) macromolecules containing ureidopyrimidinone (UPy) side-groups were synthesized. In non-polar media, it is well known that UPy groups self-associate to form hydrogen bonded dimers (DDAA); however their behavior in water-swollen hydrogels is unclear. We applied a RAFT polymerization technique to control polyHEMA's molecular weight and UPy-content, and the influence of UPy groups on water-swelling behavior will be discussed.

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Control of the inflammatory response with poly(trolox ester) antioxidant nanoparticles

Trolox is a vitamin E derivative with antioxidant properties that can be polymerized to form poly(trolox ester) (PTX), which can be further fabricated into nanoparticles. This study investigated the impact of nanoparticles based on PTX with molecular weights of 1000 (PTX-1000) and 2500 (PTX-2500) on the inflammatory response using IL-1beta stimulated immortalized rheumatoid arthritis synovial fibroblasts (MH7A cells) and PMA differentiated U937 macrophage cells as in vitro models. IL-1beta was used to induce the production of pro-inflammatory molecules and reactive oxygen species (ROS). Prostaglandin E2 (PGE2), interleukin 6 (IL-6), interleukin 8, and vascular endothelial growth factor were used as indices of inflammation. PTX-1000 and PTX-2500 nanoparticles led to a reduction in PGE2 levels at both 24 and 72 hours for both cell types. For the U937 cells, the nanoparticles lacked efficacy at 72 hours relative to 24 hours. Similarly, IL-6 levels for the MH7A cell line were decreased at 24 hours, but not 72 hours. Presumably, these results are a consequence of the slow release of antioxidant by the nanoparticles when not in the presence of carbonic anhydrase. The research conducted thus far provides evidence that antioxidant nanoparticles can serve as effective agents in the treatment of chronic inflammatory disease.

Eric Finkelstein, James H. Henderson, and Patrick T. Mather
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Cell-material interactions on an acrylate-based polymer
Shape memory polymers (SMP) are a class of polymer that can be fixed in a temporary shape, and then returned to a permanent shape through the action of an external stimulus such as temperature. SMPs with surface topography are used as active cell culture substrates. We hypothesize that shape memory polymers (SMP) are ideal for creating surfaces that mimic the topography of native tissues. An acrylate-based copolymer was synthesized to have a glass transition (Tg) near physiologic temperature (37˚C). It was determined that this material is biocompatible with bovine endothelial cells (BAEC) and bovine smooth muscle cells (BASMC). Methods for seeding cells on this material were developed and optimized. It was determined that BAECs and BSMCs grow to confluence, forming stable monolayers. These results indicate that this material has promise as a substrate for vascular cell growth to be used to model vascular cell behavior in response to shape changes.

Xinzhu Gu and Patrick T. Mather
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POSS-based thermoplastic polyurethanes for cardiovascular stent application
Shape memory polymers have been proposed for cardiovascular stent applications due to their ability to recover to a predetermined shape in vivo and to realize highly controlled deployment at body temperature as to facilitate minimally invasive surgery. The goal of this research is to develop thermoplastic SMPs with good shape recovery, optimal recovery sharpness and recovery stress pertinent to medical applications. POSS-based thermoplastic polyester-urethanes (POSS-TPU) are picked as the candidates given its good shape memory ability, and tunable mechanical property and degradation behavior based on our earlier study. Thus, a hybrid thermoplastic polyurethane (TPU) system that incorporates a poly (D,L-lactide)/polycaprolactone soft block with a hard block containing the polyhedral oligosilsesquioxane (POSS) moiety was synthesized with Tg around body temperature. The shapes recovery responses of the polymer films were extensively

studied as a function of the prior “fixing” deformation temperature (Td). The sharpness of the free recovery transition was found to depend strongly on Td. When deforming right at Tg of the materials, sharpest recovery transition was achieved. Also, highest force was generated when deforming at Tg. The tunable shape-memory responses made this polymer system potential candidate for applications in such medical devices as minimally invasive cardiovascular stents.

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Characterization of biodegradable PCL-PEO co-networks
Shape memory polymers (SMPs) are a class of stimuli-responsive materials that can undergo a shape change based on specific stimuli or conditions. Biodegradable SMPs are exciting materials because they encompass a combination of controlled degradation and triggered actuation. In this study we aimed to synthesize a biocompatible material with good shape memory properties using amphiphilic networks contained polyethylene oxide (PEO) and polycaprolactone (PCL). The tunable thermal and mechanical properties were achieved by varying the relative concentrations of polycaprolactone (PCL) and polyethylene oxide (PEO) network chains. The thermal and structural properties were investigated by wide angle x-ray diffraction (WAXD) and differential scanning calorimetry (DSC) for dry and hydrated sample. Surface degradation was induced by immersing the co-network system into lipase-containing medium. A slower degradation was observed with increasing weight percent of PEO. Furthermore, the degradation samples with high PEO content showed a significant increase in water uptake. The surface topography after enzymatic degradation revealed potential application for 3D scaffold fabrication be virtue of the appropriate length scale and high porosity. We believe this system is beneficial for applications including implantable biomedical devices, drug delivery and dynamic scaffold for cell culture.

Richard Baker, Pine Yang, James H. Henderson, and Patrick T. Mather
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Wrinkle formation directs cell morphology in culture
Cells actively probe and respond to their microenvironment. These interactions are critical during many biological processes such as angiogenesis and embryogenesis. A better understanding of how cell-material interactions influence cell behaviors would allow for the development of better tissue engineering constructs. Often, materials with micro and nano topographies or materials with differing moduli are employed for studying such cell-material interactions.
Here we investigated the use of a material capable of dynamically changing its topography in culture, and we assayed the resulting cell response. We used a shape memory polymer based bilayer system to form wrinkles after cells have attached in culture. The system was optimized to allow for wrinkle formation to be triggered upon heating to body temperature. Cells were cultured on a flat topography at 30 oC and then wrinkle formation was triggered by increasing to 37 oC. The resulting cell orientation was assayed by staining cell nuclei and cell cytoskeleton both before and after wrinkling. It was found that prior to wrinkling, cells had no preferential angle of orientation, whereas after wrinkling cells aligned parallel to the direction of the wrinkles. These results can be

used for future studies to determine the mechanisms behind dynamic cell-material interactions.

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Effect of biphasic polyurethane matrices on cell-material interactions
Extracellular matrix (ECM) provides structural and functional signals to regulate cell behavior. Understanding and replicating cell-ECM interactions on synthetic matrices is crucial for engineering tissue regenerations. Regulation of these interactions depends on matrix characteristics and therefore, it is important to design materials which can promote and maintain essential cellular functions. Biodegradable biphasic polyurethanes, which consist of hard and soft segments, can induce specific interactions between cells and matrix. Polyurethanes can be engineered to support stem cell adherence, migration, and differentiation for tissue engineering applications. In this study, we investigated the cellular responses of bone marrow derived adult human mesenchymal stem cells on amino acid based polyurethane matrices to control cell adherence, migration, and cytoskeleton structure. Preliminary results show that the different cues provided by the segmental structure of polyurethanes can control stem cell signaling and behavior. Thus, the tunable biphasic characteristics of polyurethanes are a useful tool for molecularly engineering and controlling cellular responses. Furthermore, polyurethanes can be utilized as a scaffolding material and cell delivery vehicle for inducing, maintaining, and controlling cells in 3-dimensional microenvironment. In summary, these biodegradable polyurethanes can present proper signals to support and enhance the stem cell fate for regenerative medicine.

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Characterization of primary neurite outgrowth in an electrically conductive SWCNT composite hydrogel
Neurons can re-grow following injury and are responsive to external biophysical, topographical, and/or biochemical cues (1). A physiologically compatible electrical stimulus (50 mV/mm DC) can increase neurite extension in vitro (2); however application can be attenuated when applied in vivo. This study evaluates neurite outgrowth of embryonic chick-derived dorsal root ganglia (DRG) within an electrically conductive 3D SWCNT-collagen-I hydrogel to determine compatibility of nanomaterial-laden biomaterials as a first step to retain a localized stimulus. Analysis of DRG within hydrogels in a range of nanomaterial dosages (0, 10, 50 and 100 μg/mL) did not show significant differences in neurite outgrowth ($p>0.05$). This provides initial evidence that the material is not cytotoxic. When combined with electrical stimulation, there was no significant change in outgrowth between electrically stimulated DRG (DC 50 mV/mm, 8hr, 1mA) and unstimulated controls ($p>0.05$, $n=4$). This insensitivity to the electrical stimulus is likely due to species-specific differences. For example, neonatal rat neurons are responsive to this electrical stimulus (2). Current work assesses the response of neonatal rat DRG outgrowth within a 3D supportive hydrogel in response to electric stimulation and/or nanomaterial-laden biomaterials. Initial data shows a trend towards increased outgrowth with th

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Developing dynamically tunable poly(ethylene glycol)-based biomaterials for neuronal cell control
Developing materials that can direct cellular behavior such as growth, differentiation, and migration/extension in real-time (e.g., similar to during development), will result in great progress for the development of biomaterials to direct cell function. Neural cells, similar to most cells, are sensitive to biochemical and mechanical stimuli and exploiting these cues within inert, cytocompatible poly(ethylene glycol) (PEG)-based materials may serve as excellent means to direct the repair/regeneration of neural tissues. In this study, we developed biochemically and mechanically tunable PEG-based hydrogel systems to control axon extension and branching in PC12 cells, a neuronal cell line. We investigated cellular responses on hydrogels using time-lapse microscopy tools and found that stiff hydrogels (Y = 90.5 ±0.5 kPa) resulted in 60% less cell adhesion as compared to softer hydrogels (Y = 43.0 ± 4.2 kPa). In addition, we observed that cell and axon density on hydrogels increases with increasing concentration of cell adhesion peptide (RGDS) and levels off at concentration of ~5 mM at 137.8 cells/mm2 and 4.6 axons/cell. We are currently developing novel step-growth, thiol-ene PEG hydrogels, which will allow alteration of biochemical and mechanical cues with spatial and temporal control to better mimic developmental cues and study their effects on neuronal cellular responses.

Ling-Fang Tseng, Patrick T. Mather, and James H. Henderson
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Active cell culture: a 3D programmable shape-memory scaffold
Introduction
Common tissue engineering scaffolds are static and only function as passive physical environments when used to create tissue-engineered constructs.

The objective of this present study was to use shape memory polymers in the development of a tissue engineering scaffold that is capable of controlling cell behavior via programmed shape-change.

Materials and Methods
Electrospun 3D scaffolds were prepared and employed as programmable shape changing scaffolds as follows: scaffolds were uniaxially stretched to 100% strain at 65 °C (above Tg) and fixed in the elongated state; human adipose-derived stem cells (ASCs) were cultured on the elongated scaffolds at 30 °C for 24 h; shape change was triggered by increasing the temperature to 37 °C; cells remain in culture for additional 24 h.

Scaffold structure and cell orientation and morphology were assayed before and after shape change by scanning electron microscopy and fluorescence imaging.

Results
The programmable shape-memory scaffolds undergo substantial fiber reorientation and pore size alteration. The scaffolds direct changes in cell alignment and morphology.

Conclusion
The results represent the first demonstration of 3D scaffold that can be triggered to change shape under physiological conditions with attached and viable cells.

Poster Presentations

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Engineered probiotic bacterial vesicle subunit vaccines induce robust, TH1-biased immunity

Modern recombinant vaccine engineering is increasingly focused on the development of novel delivery platforms that can address the failure of current adaptations of subunit vaccines to substantially generate both ample humoral and cellular immunity in a fashion that is broadly and realistically applicable. To address this challenge, we have engineered a flexible recombinant antigen delivery platform using engineered bacterial outer membrane vesicles (OMVs) derived from the highly immunomodulatory and traditionally probiotic E. coli Nissle 1917 bacteria (EcN). EcN OMV vaccination using a model antigen in mice demonstrated successful and robust induction of both humoral and Th1-dominated cellular immunity, and further in vitro assessment of the OMVs' ability to interface with various cellular components of innate and adaptive immunity confirmed the platform's unique and highly effective adjuvancy. These results demonstrate that by taking a biomaterials engineering approach to developing a biomolecular pathogen-like particle for vaccine delivery applications, the EcN OMV platform is capable of filling an important niche in recombinant vaccine design: direct, flexible integration of a custom recombinant antigen with effective, complete immune stimulation.

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Effects of microtopographic patterns on Escherichia coli biofilm formation on polydimethylsiloxane surfaces

Bacterial biofilms are involved in 80% of human infections and are up to 1000 times more tolerant to antibiotics than their planktonic counterparts. To better understand the mechanism of bacteria-surface interactions, polydimethylsiloxane (PDMS) surfaces with microtopographic patterns were tested to study the effects of surface topography on bacterial adhesion and biofilm formation. The patterned PDMS surfaces were prepared by transferring complementary surface topography from a silicon wafer etched via photolithography to introduce 10 μm tall square-shape features. The dimensions of protruding square features and the distance between adjacent features were systematically varied. Escherichia coli RP437/pRSH103 (with constitutive expression of red fluorescence protein) was found to preferentially attach and form biofilms in valleys between protruding features even when the dimension of plateaus (top of the square features) is

considerably larger than valleys. In addition, significant adhesion of E. coli RP437/pRSH103 cells on plateaus was only observed for 20 μm × 20 μm and larger plateaus for face-up patterns and 40 μm × 40 μm and larger plateaus for face-down patterns. These findings suggest that surface topography has significant influence on bacterial biofilm formation and a threshold dimension may be essential for biofilm formation on flat surfaces without physical confinement.

Ifeanyl Onyejekwe and Patrick T. Mather

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Nanocomposite elastomer exhibiting controlled and sustained release of nitric oxide

Nitric oxide (NO) is responsible for a number of biological functions, ranging from immune response, inhibition of platelet aggregation to neuronal communication. Due to the numerous biological functions of NO, there has been growing interest in the application of this free-radical towards improving the biocompatibility of various biomaterials. Diazeniumdiolates are synthetic NO donors, capable of holding and releasing NO under physiological conditions. Unfortunately, most diazeniumdiolates have relatively short half-lives ranging from seconds to hours, which presents a challenge when considering long-term treatment of various medical disorders. Here, we introduced the development of a novel NO-releasing elastomeric nanocomposite system capable of controlled and sustained NO release. The material was prepared by incorporating diethylenetriamine/NO (DETA/NO) into the elastomeric system. Quantification of NO was achieved by placing the system in PBS at 37 oC at a pH of 7.4 then conducted the Griess Test. The results showed remarkable controlled and sustained NO release. Incorporation of DETA/NO into an elastomeric nanocomposite system attenuated the uncontrolled and spontaneous release of NO under physiological conditions. For this reason, our NO-releasing elastomeric nanocomposite system could serve as an ideal candidate for the improvement of certain localized biomaterials applications, including thromboresistant coatings, vascular grafts and wound healing applications.

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Evaluation of a polymeric siRNA delivery system for mesenchymal stem cells (MSCs)

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Development of a fretting crevice corrosion test system for metallic biomaterials

Fretting corrosion of metallic biomaterials, including those used in modular interfaces of total joint replacements, spinal devices and even cardiovascular

stents is increasingly a major concern. The incidence and severity of fretting-related failures may depend on several factors related to mechanically assisted corrosion phenomenon. Currently, there is a need to develop and use a test system to systematically control and analyze the mechanical and electrochemical elements of fretting corrosion processes of metallic biomaterial surfaces. Such an instrument will provide detailed and quantitative information on the processes present, explore variations in materials, surface treatments; mechanical and electrochemical factors such as loading, motion, voltages and solution conditions on the process of fretting corrosion. The details of the newly developed test system and the results of a preliminary study on the effect of voltage and normal load on fretting corrosion of CoCrMo/CoCrMo couple are presented.

Shiril Sivan and Jeremy L. Gilbert
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Timelapse behavior of the cells undergoing electrochemical stress on Ti-6Al-4V
In the previous studies done in our lab, we have identified that the electrochemical potential of metallic biomaterials play a crucial role in its biocompatibility. We have observed that under cathodic potentials the cells undergo a drastic change in the cell morphology and viability. In this study we explore how does electrochemical potential of a metal surface influence cells cytoskeletal elements and ultimately the morphology. Imaging cells on opaque metal samples have always been a hurdle for the fact that we are dealing with opaque materials. We have developed a novel electrochemical chamber which would not only enable us to enforce an electrochemical potential on a metal surface, but also allow us to observe the morphological changes the cell would undergo. In brief, MC3T3 E1 pre-osteoblasts we seeded on Ti-6Al-4V surfaces and were transfected to express GFP- actin. The metal disc was then placed in a custom made electrochemical chamber. The setup was then transferred to a glass bottomed petri dish and connections to the potentiostat was made. The whole setup was them placed in an environmental chamber and an inverted microscope was used to acquire timelapse movies of the morpohological changes the cells would undergo under the influence of the cathodic potentials. For controls, no voltage was enforced.

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Injectable, nanospheres containing, Two-Solution Bone Cements (n-TSBC) with bioactive strontium hydroxyapatite (SrHA) microspheres
We have developed a two-solution bone cement containing cross-linked polymethylmethacrylate (PMMA) nanospheres (η-TSBC) for vertebroplasty and kyphoplasty. PMMA bone cements lack the ability to form chemical bonds with living bone tissue. Lately, focus has been on developing bioactive cements using hydroxyapatite (HA) and strontium as fillers, since HA is a natural bone mineral component and strontium can stimulate bone formation and act as a contrast agent. This work aims to evaluate the feasibility of making bioactive η-TSBC with strontium-hydroxyapatite (SrHA) microspheres and characterizes SrHA-η-TSBCs for their radiopacity, exothermal, and mechanical properties. SrHA microspheres

were synthesized and added to the polymer phase at the concentrations of 0, 10, 20 and 30% (w/v). The SrHA microspheres were characterized for the presence of phosphate peaks using Fourier transform infrared microscopy (FTIR), and particle size and morphology were assessed using scanning electron microscopy (SEM). X-rays (42 kV) were obtained for each cement composition and their degree of contrast was compared with η-TSBC containing 20% zirconium dioxide (ZrO2) (i.e. comparable to the commercial Kyphx (30% BaSO4)). No significant differences were found between the contrast values of 30% SrHA and 20% ZrO2 cements. The compressive properties of these cements were evaluated using ASTM standard F451-99a. This work demonstrates it is feasible to incorporate SrHA microspheres into η-TSBC and obtain sufficient radiographic contrast. The flexural and exothermal properties of these cements are still being characterized but are showing positive preliminary results.

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Fretting Corrosion Performance Test For Spinal Screw and Rod Implants

Fretting corrosion of metallic biomaterials continues to be a concern for high-load medical device applications. Mechanical factors like cyclic loading, interfacial contact and micro-motion can lead to disruption of passive oxide films on metallic surfaces. Degradation of oxide films accelerates corrosion processes, decreases structural integrity of implants and can elicit severe biological reactions in patients. In spinal devices, there has been a progressive increase in use of multi-segmental spine rod with screw fixation systems for various spinal conditions like scoliosis, spinal stenosis syndrome and post-traumatic spine instability. These constructs typically consist of multiple screws and rods with connectors, all of which lead to multiple points of metal-metal contact and high cyclic-load transmission. These constructs can have crevice-like geometries that result in restricted local environment. When these factors are combined (local fluids, fretting and restricted geometries) they may lead to significant increase in corrosion rates. In this preliminary study, the objective is to develop a highly controlled fretting corrosion performance test method for spinal devices that can control, monitor and assess the electrochemical processes present at fretting interfaces in terms of current and voltage response. We investigate in vitro corrosion and fretting behavior of spinal rod-screw constructs under physiological loading conditions. This helps us determine the onset motion/load required to induce fretting corrosion and the magnitude of the electrochemical response at specific cyclic displacements.

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Development of a pro-angiogenic biomaterial: peptide identification, synthesis and preliminary screening

Pro-angiogenic biomaterials are a promising therapy for treating ischemic tissue disorders such as cardiac ischemia, which was the leading cause of death worldwide in 2008, killing more than 7.2 million people [1]. In developing angiogenic biomaterials, naturally occurring proteins are commonly employed.

However, these proteins have low stability in vivo, and simple injection into target tissue is not sufficient to maintain localized, therapeutically-relevant protein concentrations, necessitating the use of a delivery system. However, due to their large size, proteins can only be integrated into biomaterials at low concentrations, resulting in short-term delivery and/or poor efficacy. To circumvent the issues associated with large proteins, eleven small peptide sequences which mimic their angiogenic activity have been identified. These sequences were synthesized via solid phase fluorenylmethyloxycarbonyl (Fmoc) chemistry, and synthesis confirmed by matrix-assisted laser desorption ionization time of flight (MALDI-ToF) mass spectrometry. The angiogenic potential of these peptides is being tested via the human umbilical vein endothelial cell (HUVEC) proliferation and tube formation assays. Future work will involve developing controlled release strategies for the angiogenic peptides, tethering peptides to poly (ethylene glycol) (PEG) hydrogels with tissue-responsive chemistries. We aim to investigate the biomaterial's angiogenic effect using the chick chorioallantoic membrane (CAM) assay

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Patterning of siRNA cues within hydrogels to spatially control mesenchymal stem cell differentiation

Spatial control of mesenchymal stem cell (MSC) differentiation is critical for the engineering of complex tissue structures for many applications within regenerative medicine. We ultimately aim to control MSC gene expression and differentiation through the patterning of small interfering RNA (siRNA) cues within MSC-laden poly(ethylene glycol) (PEG) hydrogels. We utilize PEG because it provides an advantageous scaffold for MSC encapsulation and culture, offering biocompatibility and maintenance of MSC viability over the time course of differentiation and tissue evolution. We are using a previously-developed siRNA delivery system to characterize gene expression of MSCs encapsulated within hydrogel networks. LIVE/DEAD imaging revealed that MSCs remained viable within nanoparticle containing hydrogels after 48 hours. Preliminary results showed a lack of significant difference in gene expression between siRNA treated and untreated hydrogel regions; however diffusivity analysis indicated that this was not attributable to siRNA nanoparticle diffusion within the hydrogel, but may be due to poor cell-material interactions as these interactions have previously been shown to be critical to proper cell function. Therefore, we are now introducing biochemical functionalities to determine if siRNA-patterned hydrogels with better cell-material interactions provide the potential to spatially control MSC gene expression.

Pushkar Varde and Julie M. Hasenwinkel

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Fabrication and characterization of crosslinked hyaluronic acid hydrogels for tissue engineering applications

The purpose of this study was to fabricate and characterize crosslinked hydrogels based on Hyaluronic acid (HA) for potential use as tissue engineering scaffolds to enhance axonal regeneration. HA is a linear polysaccharide consisting of alternating 1, 4- linked units of 1, 3-linked glucoronic acid and N-acetylglucosamine [1-4]. It is one of the several glycosaminoglycan components of the extracellular matrix and has sites that bind to cell surface receptors (CD44, RHAMM) [4,5]. The molecule has several sites that can be derivatized to attach moieties that can be crosslinked using different strategies. We aim to exploit this avenue to fabricate and characterize gels crosslinked at different monomer and crosslinker concentrations. Sodium salt of HA was derivatized at one of its hydroxyl sites with excess of Gylcidyl Methacrylate (GMa) to form methacrylated HA (HAGMa). Crosslinking was then performed using varying concentrations of the HAGMa and polyethylene glycol diacrylate (PEGDa), a bifunctional crosslinker, in the presence of a photoinitiator and a UV source. The crosslinked hydrogels were swollen to equilibrium before being tested. The hydrogels were characterized to evaluate their Young's modulus of elasticity, swelling behavior, rheological properties and microstructure. It was observed that the gels are porous and the pores appear to be interconnected. The modulus of the hydrogels increased, while the swelling coefficients decreased with increasing crosslinker concentrations. Further studies are under way to characterize the rheological properties of the pre-crosslinking solution to understand the relaxation behavior of the HA chains.

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Tuning recovery kinetics of a shape memory polymer for active cell culture

Topography has been shown to be a powerful regulator of cell behaviors, such as cell alignment. We recently developed a biocompatible shape memory polymer (SMP) substrate that can change topography on command. To investigate diverse cellular responses, control of the rate of topographic changes is desirable. The objective of the present study was to enable such control through tuning of the recovery kinetics of a biocompatible SMP at body temperature (37 °C). The glass transition temperatures (Tg) of eleven different copolymer compositions were found by differential scanning calorimetry. We found that as the concentration of one monomer was increased, the transition temperature increased from 44 °C to 51 °C. Plasticized samples were found to have Tgs from 42 °C to 46 °C. In addition, a uniaxial strain was fixed into the SMP to measure the recovery as a function of time at body temperature by dynamic mechanical analysis. Recovery experiments performed revealed that as the composition of one monomer increased the rate of recovery at 37 °C decreased.

The successful tuning of the Tg and recovery rates of the SMP used should allow us to further study the effects of dynamics on active cell culture.

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Development of a novel bone-targeted polymer therapeutic

Our goal is to utilize the living polymerization technique, reversible addition-fragmentation chain transfer (RAFT), to create poly(ethylene glycol) (PEG)-based polymers capable of bone-targeted delivery of drugs. Specifically, we are interested in delivering 6- bromoindirubin-3'-oxime (BIO) to bone resorption sites to exploit its ability to enhance osteoblast bone production. To create a BIO delivery system, we have synthesized PEG-based macromers to controllably release BIO from polymers via hydrolytically degradable ester linkages. Using these macromers, we synthesized RAFT polymers with 5% and 10% BIO with overall PDIs of 1.3 or less and have shown that BIO release is sustained for up to

2 weeks. Moreover, the end groups present in RAFT polymers enable us to effectively functionalize our polymer chain ends with the bone resorption pit-homing peptide, TPLSYLKGLVTVG, to target the polymer therapeutic specifically to bone resorption sites. This peptide has been synthesized using solid phase peptide synthesis and analyzed for correct molecular weight via matrix-assisted laser desorption/ionization time of flight (MALDI-TOF). Native gel electrophoresis has demonstrated this peptide interacts with tartrate resistant acid phosphatase (TRAP), a molecule deposited by osteoclasts in bone resorption pits during bone turnover. We are currently synthesizing peptide-functionalized CTAs to realize resorption pit targeted BIO delivery.