Authors	Abstract Title	Abstract
Nicole Durig, BS; Melinda Harman, PhD	Characterizing Metal-Polymer Bearing Couples: Assessment of Knee Replacement Prostheses Retrieved After In Vivo Function	Efforts to enhance knee replacement longevity include improving the polyethylene bearing materials and modifying the hardness and scratch-resistance of metallic femoral components. In vitro wear simulations have established links between increased surface roughness (e.g. scratches) and increased wear rates for polyethylene bearings, but such links have not been widely studied in vivo. The purpose of this study is to characterize surface roughness and damage on actual prostheses retrieved after knee replacement in patients. Twenty-two bearing couples, inclusive of ten different knee prosthesis designs, were retrieved after 10 to 224 months of in vivo service in patients. Articular surface damage on the bearing couple was assessed using quantitative optical stereomicroscopy. Femoral component surface roughness was quantified using a non-contact surface profilometer applied in a uniform 3-dimensional grid of 40 equally spaced measurement points covering the entire metal articular surface. Preliminary data (n=10) reveal an average surface roughness (Ra) of 29.9+11.0 nm for the metallic femoral components and an average damage area of 49.8+14.9% for the polyethylene bearings. The preliminary data support a linear correlation between roughness and damage area for these retrieved bearing couples (R2=0.8). These observations characterize a potentially adverse tribological environment in these retrieved knee prostheses.
Bo Wang, Clara Esteban Perez, Alayne Stewart White, Filip To, Amy Curry, and Jun Liao	Myocardial Scaffold-based Cardiac Tissue Engineering: Application of Coordinated Mechanical and Electrical Stimulations	Tissue engineered cardiac patch has great potential for ventricular wall reconstruction. In this project, we designed a multi-stimulation bioreactor that can provide coordinated mechanical and electrical stimulations for facilitating cardiac patch development. The bioreactor consists of one tissue culture chamber. The linear movement was applied by a Xslide assemblies step motor. Electrodes were made from Teflon-coated silver wire. The frequency and amplitude of both cyclic stretch and electrical pulse were controlled digitally with a custom LabView program. For recellularization, the acellular porcine myocardial scaffolds were seeded with MSCs (106/ml) by needle injection, and subjected to bioreactor conditioning. 5-azacytidine treatment (3 μmol/L, 24-hour) was applied to promote myogenic differentiation. After two-day culture with mechanical (20% strain) and electrical stimulation (5 Volt, 1 Hz), high cell density and good cell viability were observed in the reseeded scaffold. Immunohistological staining studies showed that the differentiated cells demonstrated cardiomyocyte-like phenotypes. Mechanical testing demonstrated that a large degree of tissue remodeling took place after 2-day bioreactor conditioning. In conclusion, we have successfully built a bioreactor that is able to apply mechanical and electrical stimulations in cardiac patch engineering. We found that cardiomyocyte differentiation and tissue remodeling were largely promoted with the coordinated simulations.
Amanda L. Glover, James B. Bennett, Joel N. Glasgow, Jacqueline A. Nikles, Christopher S. Brazel, David E. Nikles	Drug Release and Cell Targeting of Poly(ethylene glycol-b-caprolactone) Magnetomicelles	A delivery system for the anti-cancer drug doxorubicin has been developed using diblock copolymer poly(ethylene glycol-b-caprolactone) self-assembled micelles. The copolymer nanoparticles, or micelles, have been designed with semicrystalline cores, verified by differential scanning microcalorimetry. A process has been developed where doxorubicin and magnetite nanoparticles were loaded into the micelles' cores and a targeting peptide, cRGDfk, was attached to the corona of the micelles. Drug release experiments performed under isothermal conditions at 37 °C and 57 °C showed enhanced drug release at temperatures above the melting point of the micelles' core. This supports the proposed idea that when the cores of the micelles are melted, more drug is able to diffuse from the previously semicrystalline core of the micelle. The mechanism of heating in the human body will be magnetic induction using iron oxide nanoparticles. The targeting ligand has also been attached to the corona of the micelles through the Michael addition of the thiol terminus of the peptide to a maleimide terminated PEG-b-PCL. Preliminary cell studies showed that at a 5 μL dose the peptide terminated micelles bound more effectively to HEK293 cells than the non-targeted micelles.
Matthew Phipps, Yuanyuan Ma, Will Clem, Susan Bellis	Delivery of PDGF-BB from a Bone-Mimetic Electrospun Scaffold	The recruitment of Mesenchymal Stem Cells (MSCs) into a skeletal defect is a vital step in the bone healing process. Once present at the site of bone repair, MSCs differentiate along the osteoblastic lineage, producing tissues necessary to heal the defect. Sustained local delivery of a MSC chemotactic factor from a biodegradable substrate offers a method to stimulate robust MSC recruitment into the site of implantation. In the current study, PDGF-BB was found to be the most effective factor tested in stimulating MSC migration. Furthermore, bone-mimetic electrospun scaffolds of polycaprolactone, collagen I and hydroxyapatite (PCL/col/HA) were able to adsorb and subsequently release higher levels of PDGF-BB over an 8-week interval as compared to scaffolds of PCL alone. Additionally, the PDGF-BB released from PCL/col/HA scaffolds retained bioactivity, promoting MSC migration in a transwell assay and modified scratch assay. Previously, we reported the ability of PCL/col/HA scaffolds to support greater MSC adhesion, proliferation and activation of integrin-related signaling cascades than PCL scaffolds, making them a promising osteoconductive matrix for growth factor delivery. Ultimately, the delivery of the chemotactic molecule PDGF-BB from a porous, biodegradable, bone-mimetic matrix shows promise in stimulating MSC migration and supporting new bone formation at the site of implantation.
Chris E. Nelson, Elizabeth J. Adolph, Mukesh K. Gupta, Fang Yu, Jeffery M. Davidson, Scott A. Guelcher, Craig L. Duvall	Tunable Local Delivery of siRNA from Injectable Scaffolds in vivo	Small interfering RNA (siRNA) can be utilized to achieve gene specific silencing, however siRNA is rapidly degraded by nucleases, is membrane impermeable, and has transient activity. Here, a novel system is presented for sustained, tunable release of pH-responsive, micellar, siRNA-loaded nanoparticles (si-NPs) from an injectable polyester urethane (PUR) scaffold. The si-NPs consisted of a diblock copolymer that self-assembles into 40nm micelles with a cationic corona (ζ=19mV) capable of siRNA electrostatic loading and a pH-responsive core that mediates escape from endo-lysosomal pathways. It was shown that si-NPs were successfully loaded into PUR scaffolds (si-NP-PUR) which efficiently release >80% of their payload and gene silencing bioactivity was maintained post-release (50% gene silencing). Furthermore, it was found that excipients could be utilized to control the rate of si-NP release from the scaffold in vitro and in vivo. Histology revealed that the si-NP-PUR were biocompatible and supported cell infiltration with no signs of toxicity. These combined data demonstrate the potential for this local siRNA delivery technology to be used as a research tool for elucidating effects of long-term local gene silencing. In addition this platform can be potentially used therapeutically for sustained local silencing of aberrant genes within chronic wounds and other tissue defects.
Hongmei Li, Shann S. Yu, Martina Miteva, Chris E. Nelson, Todd D. Giorgio, Craig L. Duvall*	MMP-Responsive, Proximity-activated Targeting Polymeric Nanoparticles for siRNA Delivery	A smart polymeric nanoparticle (SPN) with matrix metalloproteinase-7 (MMP-7) dependent proximity-activated targeting (PAT) has been designed and tested for targeted intracellular siRNA delivery to MMP-7 overexpressing tissues (i.e., tumor metastases). With this novel PAT-SPN design, a removable PEG corona mitigates cytotoxicity and nonspecific uptake in normal tissues. Exposure to MMP (in proximity to a tumor) unmasks the underlying cationic layer that mediates cellular uptake. Finally, pH-responsiveness from the particle core assists escape from endo-lysosomal pathways and promotes access to cytoplasmic RNAi machinery. Here, it was verified that the PAT-SPN produced increased cell uptake and siRNA activity when it was "pre-activated" by MMP-7. This PAT-SPN design shows significant promise for targeted siRNA delivery to cancer metastases.

Yu Cao, Shuangcheng Tang, Samuel Goddard, Wei He	Thermal and pH Responsive Polymers based on Functional Derivatives of N-vinyl-2-caprolactam for Smart Drug Delivery	A series of new dual stimuli responsive polymers containing functionalized N-vinyl-2-caprolactam (VCL) were studied. VCL derivative, 3-(tert-butoxycarbonyl)-N-vinyl-2-caprolactam (TBVCL) was synthesized and copolymerized with VCL to obtain copolymers with different molar compositions (COOH-PVCL9 and COOH-PVCL14). The structure and composition of copolymers were determined by nuclear magnetic resonance (1H-NMR), Fourier transform infrared spectroscopy (FTIR), and thermogravimetric analysis (TGA). Due to the close structural similarity of the two monomers, improved compositional control of the copolymers was achieved. Reactivity ratios of these two monomers were also characterized by the NMR method. Sharp and complete phase transitions of the copolymers were shown to be pH-dependent, with cloud points ranging from 35 °C to 44 °C for COOH-PVCL9 and 29 °C to 64 °C for COOH-PVCL14 upon pH change from 2.0 to 7.4. Using NIH/3T3 fibroblast, the functionalized PVCL copolymers were shown to be biocompatible up to 2 mg/mL. Additionally, 3-(tert-butoxycarbonylmethyl)-N-vinyl-2-caprolactam (TBMVCL) was synthesized and copolymerized with VCL to achieve dual responsiveness. This new series of functional VCL-based water soluble copolymers with tunable responsive properties provides a new option to the growing list of biocompatible polymers for smart drug delivery.
Emilia Smith, Ashley Cornell, Keisha Walters	Determining Diffusion Coefficients of Asthma Drugs through Artificial Pulmonary Mucus Using ATR-FTIR Methods	Aerosols are a common method of drug delivery to treat pulmonary illness, such as asthma, and offer several advantages over traditional drug delivery routes. Smaller required dosages, chemical stability, and fast response are some benefits of direct delivery to the pulmonary system via the airways. In this study, the diffusion coefficients of two common asthma medications, theophylline and albuterol, were measured and compared to the diffusion coefficients of drugs through native porcine mucus. The physiological system was modeled using an artificial mucus layer with the theophylline and albuterol dissolved in isopropanol. Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR) was used to measure the drug concentration at one surface of the artificial mucus by observing increases in peak height as the drug diffused. This peak height data was converted to concentration, and Fick's Second Law of diffusion was used to solve for the diffusion coefficient of the drug through the artificial mucus. The diffusion coefficient of theophylline was found to be 0.41-0.53 x 10-5 cm2/s and the diffusion coefficient of albuterol was found to be 1.5-3.2 x 10-5 cm2/s. In future work, the same methods will be employed to measure the diffusion coefficients of nanoparticles through pulmonary mucus.
Bonnie K. Culpepper and Susan L. Bellis	Functionalizing allograft bone by exploiting a heptaglutamate domain to anchor bioactive peptides	There are more than 2.2 million bone grafts performed each year, and autologous bone grafting (the gold standard) is limited clinically by available quantity and quality of bone. Allograft bone is a common alternative, but regeneration capacity is limited. The processing and sterilization steps necessary to reduce the immune response to allograft bone is thought to denature and destroy many proteins and growth factors. We aim to enhance osteoinductivity by functionalizing allograft bone with bioactive peptides: DGEA (collagen-mimetic) or BMP-2pep (from knuckle domain of BMP-2 protein). In order to facilitate reliable tethering of these peptide domains we have explored the use of a hydroxyapatite (HA) binding domain ("E7") and found that the E7 domain directed significantly more peptide to the surface of allograft and enhanced peptide retention in vitro. Moreover, E7-DGEA was retained in vivo for at least three months, highlighting the potential of this mechanism as a sustained delivery system for bioactive peptides. While this study focused on DGEA and BMP-2 peptides on allograft bone, we believe the E7 domain could be used to anchor various peptides to any type of HA-containing material to enhance cell adhesion, differentiation, or vascularization.
Amanda Clark, J. Zach Hilt, David Puleo	Effect of Processing Temperature on Poly(lactic-co-glycolic acid) Scaffold Properties and Bioactivity of Insulin-like Growth Factor I	Poly(lactic-co-glycolic acid) (PLGA) is commonly used as a scaffold because it exhibits biodegradable and biocompatible properties. PLGA allows for the encapsulation of growth factors, such as insulin-like growth factor I (IGF-I), which has been shown to stimulate the synthesis of proteoglycan and type-II collagen while enhancing chondrocyte matrix synthesis. The objective of this study was to determine if there is an effect on IGF-I bioactivity as a result of elevated temperatures used during the fabrication of IGF-I encapsulated PLGA scaffolds. In this study an IGF-I solution was incubated at various temperatures to order to find the range at which IGF-I bioactivity is preserved. To evaluate the bioactivity of IGF-I, this solution was cultured with SaOS cells and monitored for DNA synthesis in comparison to the control. It was found that IGF-I could withstand up to 50°C and maintain bioactivity. Afterwards, the IGF-I was encapsulated into PLGA microspheres using a W/O/W emulsion and fabricated into scaffolds, from which the release profile was measured. The released supernatant was also incubated with cells, and the results verify that the IGF-I bioactivity was not lost due to scaffold fabrication. As a final evaluation, bone marrow cells were seeded onto the scaffolds encapsulated with IGF-I to evaluate the effect of the added IGF-I, which showed an increase in GAG and DNA content at 3 and 4 weeks as compared to the blank scaffolds.
Robert Rudd, Dr. David Puleo	PLGA Scaffold Modification for HBP-Drug Conjugation, Binding, and Controlled Release	The objective of this study was to investigate a novel system for delivering drugs into a bony wound site. Porous poly(lactic-co-glycolic) acid (PLGA) scaffolds were fabricated then mineralized by submerging them for four days in simulated body fluid. Following mineralization, hydrazine bisphosphonate (HBP) molecules were bound to the mineralized scaffolds. A model drug was then attached to the HBPs to measure controlled release via acid-labile bonds. SEM images confirmed that mineral globules formed on the surface of the scaffolds, and X-ray diffraction showed that the mineral had a similar crystalline structure to that of hydroxyapatite. Once the mineral was characterized, isotherms for binding of HBPs to the mineralized scaffolds were created. As expected, HBP binding increased with HBP concentration in a sigmoidal manner. Based on these results, conjugation to and hydrolytic release of 4-nitrobenzaldehyde (used as a model drug) from HBP adsorbed on the scaffolds were measured. Because of the wide range of applications, these mineralized scaffolds have the potential to serve as a platform for controlled drug release via acid-labile bonds to elicit many physiological responses.
Daniel G. Abebe and Tomoko Fujiwara	MECHANISTIC STUDIES ON MICELLAR STRUCTURES OF PLA-PEG-PLA TRIBLOCK COPOLYMERS TOWARDS WELL-CONTROLLED STEREOCOMPLEXED HYDROGELS	Thermo-responsive biodegradable hydrogels have been developed for drug delivery systems and temporary implants. The physically cross-linked, thermo-responsive hydrogels derived from the mixture of two enantiomeric triblock copolymers, PLLA-PEG-PLLA and PDLA-PEG-PDLA were first reported by Fujiwara and Kimura in 2001. This PLA-PEG-PLA stereocomplex hydrogel, however, showed relatively low storage modulus (ca. 1,000 Pa) and thus, was insufficient for many applications as injectable implant materials. Modification of molecular weight and micellar structure significantly improved the mechanical strength of these hydrogels. Micelles composed of block copolymers with different PEG block length are shown to possess unique and different properties from the micelles composed of block copolymers with the same PEG block length. These mixed copolymer micelles show a controllable sol-gel transition at wide temperature range between 4 and 80oC. Sol-gel transition at around body temperature is achieved by adjusting the copolymer ratio. The resulting hydrogels exhibit storage modulus significantly higher than those previously reported.

Norowski, PA. Babu, J. Haggard, WO. Eckstein, EC. Padatrow, AC. Bumgardner, JD.	Antimicrobial activity of minocycline-loaded genipin-crosslinked nano-fibrous chitosan mats for guided tissue regeneration.	Antimicrobial delivery has been advocated for guided tissue regeneration (GTR) or guided bone regeneration (GBR) therapies involving patients with aggressive or unresolved periodontitis/peri-implantitis. Electrospun chitosan membranes demonstrate several advantages over traditional GTR barrier membranes because they stimulate healing, mimic the topology of the extracellular matrix, and allow for diffusion of nutrients and wastes into/out of the graft site. In this study, minocycline was incorporated into 5 or 10 mM genipin-crosslinked or uncrosslinked chitosan membranes by passive absorbtion at 5 or 10 mg/mL. The minocycline-loaded membranes and control membranes (carrier only) were tested against Porphyromonas gingivalis (P. gingivalis) by repeated zone of inhibition measurements. Results showed that minocycline loading resulted in bacterial inhibition for up to 8 days. Crosslinked membranes resulted in an extended release of minocycline as compared to uncrosslinked membranes (8 days compared to 4days). Biocompatibility testing was conducted over 5 days using SAOS-2 osteosarcoma cell line and CellTitre GLOTM luminescent cell viability assay (Promega, Madison, WI). Results demonstrated that the genipin crosslinking of the membranes was not cytotoxic and did not affect osteoblastic cell proliferation. These in vitro results suggest that minocycline-loaded genipin-crosslinked electrospun chitosan membranes may be efficacious in reducing early bacterial contamination of GTR graft sites.
Jennings, JA; Hassan, MM; Courtney, HS; Bumgardner, JD; Haggard, WO	Local Delivery of Anti-biofilm agent Cis-2 Decenoic Acid	Treatment of infection resulting from bacterial biofilm can be problematic. A signaling molecule has been identified, cis-2 decenoic acid (C2DA), which induces dispersion of bacterial biofilms, inhibition of biofilm formation, and inhibition of bacterial growth. These characteristics make C2DA an attractive candidate for local delivery to prevent infection. Because of its hydrophobic nature, the fatty acid is not water soluble, which presents difficulties in incorporating it into traditional drug delivery vehicles. In this study chitosan sponges were loaded by direct incorporation of C2DA (fabrication loading) or passive uptake of C2DA solution (Point-of-care loading). Sponges were placed in 10 mL phosphate buffered saline (PBS) in Wheaton vials and placed in a 37°C incubator. Eluates were sampled and the PBS was completely refreshed at each sampling point. C2DA concentration was quantified using HPLC. Point-of care loading of C2DA into chitosan sponges results in the highest concentrations released. The addition of emulsifying agents slightly improved the release of fatty acid from fabrication-loaded chitosan over C2DA alone, but the average quantity released does not reach levels found to be inhibitory to biofilm formation in vitro. Further testing is required to determine the effect of cosolvents on biofilm-inhibitory activity, and to establish in vivo efficacy.
Xiaohua Huang	Gold nanorods for photothermal therapy of cancer	Gold nanorods are a novel class of contrast agents for photothermal cancer therapy due to their strong surface plasmon absorption properties in the near infrared region. They preferentially accumulate into tumors after systemic administration and subsequent irradiation with near infrared light create heat capable of destroying cancer tissue. We present here our recent studies on the development of gold nanorods for photothermal treatment of head and neck cancer including both in vitro cellular studies and in vivo animal studies using mouse xenograft tumor models.
Shann S. Yu, Cheryl M. Lau, Whitney J. Barham, Halina M. Onishko, Christopher E. Nelson, Hongmei Li, Fiona E. Yull, Craig L. Duvall, & Todd D. Giorgio	In Vivo, Macrophage-Specific RNAi Targeting via 'Click', Mannosylated Polymeric Micelles	Macrophages represent an important therapeutic target, because their activity has been implicated in the progression of common, debilitating diseases such as cancer and atherosclerosis. However, macrophage-specific drug delivery within pathologic sites is a significant challenge, as non-specific drug delivery may lead to side effects and undesired interference with molecular mechanisms in healthy tissues. Because CD206 (mannose receptor) is almost exclusively expressed on macrophages and dendritic cells, and upregulated in tumor-associated macrophages, we designed and characterized pH-responsive, mannosylated polymeric micelles in order to achieve CD206-targeted drug delivery. The glycoconjugates improved siRNA delivery into primary murine macrophages by fivefold relative to a non-targeted carrier. Internalization of these constructs can be blocked by co-incubation with mannose or suppressed by downregulation of CD206 via LPS. The delivered siRNA retained its activity following delivery, resulting in 40±10% knockdown of a model gene within 4h of delivery. Additionally, the glycoconjugates were avidly recognized and internalized by human macrophages, and facilitated the delivery of 13-fold more siRNA into these cells relative to model cancer cell lines. Preliminary results also show that the glycoconjugates co-localize with CD206 in murine breast tumors in vivo, suggesting that these vehicles may become an enabling technology to target macrophage activity in tumors.
Leah Nunez, BS; Melinda Harman, PhD	Training for Non-Destructive Analysis of Ultra High Molecular Weight Polyethylene Joint Replacement Bearings	In order to evaluate the impact of physiological loading on medical devices, the mechanisms of failure must be fully investigated. For failed implants recovered from joint replacements, proper evaluation of ultra-high molecular weight polyethylene (UHMWPE) requires a detailed analysis of the different types of damage affecting different portions of the implant's bearing surface. This study will implement a Damage Mode Atlas to train new researchers in accurate assessment methods for determining UHMWPE damage pattern modes while improving their inter-rater reliability. The Damage Mode Atlas is a pictographic atlas that serves as a supplementary tool for conducting Stage II non-destructive analysis of explanted UHMWPE bearings. This study will incorporate an instructor-led active leaning component in which the students will be trained to evaluate damaged UHMWPE implants using optical microscopy. Once the training has been effectively implemented, hypothesis driven research will be initiated using forty-three UHMWPE implants retrieved from patients during revision total knee replacement. Through examination of the bearing surface, we hypothesize that the areas affected by different damage modes will vary considerably between different bearing materials (cross-linked UHMWPE) and designs (articular constraint). These factors can then be targeted for improving polymer bearings in joint replacement applications.
Elizabeth Burghardt, Melissa Dunphy, Kaitlin Grove, Nadine Luedicke, Molly Townsend, Delphine Dean, PhD, Jiro Nagatomi, PhD.	Re-Engineering of Central Venous Catheterization Simulator	Our project comes from an undergraduate group focused on re-engineering a simulator for Central Venous Catheterization (CVC) procedures. CVC involves the insertion of a catheter through the subclavian vein or jugular vein and into the heart. With the target veins so close to the lungs and vital arteries, imprecision is fatal. Currently available simulators are expensive, inconvenient, and often anatomically inaccurate. Shortcomings of existing designs include the lack of a rotatable head, necessary anatomical landmarks, and a mechanism for proper patient orientation prior to the procedure. Through collaboration with an expert in medical simulation these issues have been addressed. Further complaints include a lack of reflection of common approach techniques. A clinician performing CVC is guided either by palpation or ultrasound. The tissue analogue of our simulator is key in effectively simulating this important aspect of the procedure. The ultrasoundability, along with its flesh like feel and stability at room temperature are distinct characteristics of the material. Thus, the tissue analogue is applicable to other needs beyond the CVC simulator. The tissue analogue and the simulator as a whole are in the process of being patented. Future work includes distribution of the simulator and expansion into other simulators.

Uvarov, O., Mattix, B., Pollard, S., Reese, L., Alexis, F.	Effects of Polymeric Nanoparticle Surface Properties on Interaction with Brain Tumor Environment	In 2012, an estimated 577,000 people will die from cancer in the US alone. Current cancer treatments such as chemotherapy and radiotherapy are mostly effective, but posses their own advantages and disadvantages. One method to improve current drug delivery is using nanocarriers to specifically target cancerous cells, minimizing harmful side-effects to healthy cells. The surface of the carriers can be modified to change their interactions with the biological environment, controlling biocirculation and carrier degradation. However, not enough is known about how nanoparticle functionalities manipulate its interactions with the cancerous environment. The goal of this study is to identify nanoparticle surface properties that will maximize the efficacy of drug delivery to brain cancer cells. Poly(lactic acid)-poly(ethylene glycol) (PLA-PEG-R) particles were chosen for their biocompatibility and biodegradability for testing with twenty five functional groups. Tests were conducted with human brain cancer cells (U87 and U138) and control cells (human lung and breast cancer, HBMEC, and HUVEC). Interaction with three biological systems was studied: extracellular matrix, intracellular proteins, and cellular uptake. Results show that different functional groups have a significant effect on the bioactivity of the nanocarriers and that their interactions with the environment are much more complex than the standard electrostatic interactions.
Erik A. Hammes, Tyler G. Harvey, Elliot D. Mappus, Amanda K. Nguyen, Brian D. Peterson	3T3 Fibroblasts Solving Mazes in Response to Growth Factor Concentration	In wound healing, fibroblasts migrate to the site of injury and serve an integral role in repairing and healing the wound. As tissue engineering develops into a potential tool for regenerating damaged and diseased tissue, an understanding of the fibroblast migration mechanism and the effects of fibroblast growth factor is vital. Cellular navigation through the extracellular matrix in vivo requires recognition and avoidance of obstacles. In order to study the migration mechanism, we examined the process of wound healing interrupted by a physical barrier when two leading edges of fibroblasts are separated by a maze of polydimethylsiloxane (PDMS). The maze was attached to the bottom of a cell culture dish and fibroblast cells were plated on two access points on opposite ends of the maze. Observations of the growth of the fibroblasts occurred for 48 hours after the opening of the entrance to the maze. The results of these studies will be compared to mathematical models of cell growth in response to chemical soluble factors. Our long-term goals is to build a model to predict cell growth and migration in 3D that can be used to help design novel wound healing therapies.
Phillip Gould, Anita Patrick, Theresa Hafner, Delphine Dean, and Marian Kennedy	South Carolina	Unlike bone, teeth exhibit very poor native tissue repair mechanisms; there is very limited repair of damaged dentin by odontoblasts and almost no repair of enamel after damage Our long-term goal is to understand how to engineer and design material that can push dental cells to repair damaged dentin and enamel. In our current study, we are subjecting dental pulp stem cells to different topographical substrates to analyze their migration, proliferation, and morphology. To begin the studies, the cells were plated onto micropatterns created using lithographic techniques. There will be four different types of patters: lines, circular holes, circular bumps, and hexagonal honeycomb patterns. The line and circular patterns are similar to patterns used by other researchers with bone marrow cells. The hexagonal pattern was selected because it mimics the hexagonal structures found in natural dentin. Initial results show that, after a five-day culture period, osteoblasts tend to migrate off some of the patterns. In addition, we predict that the dental cells will also migrate towards the patterns edges. With knowledge of how stem cells migrate and differentiate we can create better tissue engineering replacement therapies in the dental world and beyond.
Benjamin Stoner, Rachel Morrison, Bre Przestrzelski, Jhilmil Dhulekar, Robert Lewis, Erika Jelen, Thomas Moore, Dr. Dan Simionescu, Dr. Agneta Simionescu, Dr. Chris Recknor, Dr. Frank Alexis	Targeted nanoparticles to deliver drugs through controlled release kinetics to bone tissue	Osteoporosis, the loss of bone density and thinning of bone tissue, is the most common bone disease and affects 20% of women ages 65-74, and >50% of women over 85. One treatment paradigm is to stimulate bone formation. We aim to develop a bone-targeting, FDA-approved, bioactive nanoparticle drug delivery system (NPDDS) to stimulate bone formation for osteoporosis therapy. The NPDDS is comprised of a hydroxyapatite core coated with poly(glycolide)-poly (ethylene glycol) (PGA-PEG) copolymer to encapsulate and release drug. Preliminary studies have shown that lovastatin stimulates alkaline phosphatase expression and promotes extracellular calcium production. Concurrently, we have developed a bone targeting ligand and have fully characterized the NPDDS. Future aims of this project include validating the effectiveness of lovastatin as a viable bone growth drug using 3D cell cultures with alkaline phosphatase and BCA assays, Presto Blue, and extracellular calcium production. Also, we will evaluate the effectiveness of the NPDDS on osteoblast activity in vitro. Finally, our team will be optimizing the conjugation of the bone targeting biomolecule to the nanoparticle and determining the biodistribution and targeting efficacy in vivo.
Alex Cusick, Kaitlin Grove, Qi Guo, Margeaux Rogers, Kayla Perry, Haley Scruggs, Dr. Delphine Dean, Dr. David Kwartowitz	Ultrasound Probe Design for Better Rotator Cuff Injury Diagnosis	Abstract: Rotator cuff injuries affect more than 90% of the US population. Treatment ranges from physical therapy to surgery. However, it is often difficult to determine which initial injuries will respond to physical therapy and which will deteriorate and need surgery. One of the primary tools for rotator cuff diagnosis is ultrasound imaging. The advantage of ultrasound is that it is portable, safe, and relatively cheap compared to other imaging modalities including CT and MRI. While ultrasound is good at distinguishing soft tissues in real-time, it lacks anatomic context particularly in saved image data. Therefore, the goal of our project is to design a new instrumented ultrasound probe that would measure transducer position and angle, which could be tagged to the specific image. In addition, our design includes pressure transducers to quantify the amount of force that the ultrasound technician applies to the patient during imaging. This data can be used to estimate tissue modulus. Our long-term goal is to predict rotator cuff tears and long-term prognosis using the calculated tissue modulus and annotated images. This could help inform clinicians and lead to more accurate diagnoses.

Ramona Soileau, Andy Whitten, Jacob Cartner	Fatigue Characteristics of Orthopaedic Biomaterials	The overall mechanical properties of titanium and stainless steel biomaterials are well known, but a purview of the literature indicates that comparing their biomechanical fatigue performance may be application dependent and is evaluated at high cycle counts. The purpose of this study was to utilize a standardized methodology to compare the mechanical performance of stainless steel and titanium orthopaedic trauma implants in a trauma lifecycle fatigue scenario of no more than one million cycles. One hundred twenty three (123) intramedullary nail coupons composed of either cannulated ASTM F138 316L stainless steel rod stock (n=69) or cannulated Ti-6Al-4V alloy rod stock (n=54) were prepared with a 32µin. maximum surface finish. The specimens were tested in the most critical physiological condition by isolating a transverse screw hole and subjecting to four-point bend sinusoidal cyclical fatigue at multiple load levels until failure or run-out to one million cycles. Varied load levels were utilized during testing to gain a trend between stress level (range: 480–2200 MPa) versus fatigue survival, with multiple specimens (up to n=10 per load level) tested for comparison. This study shows that fatigue survival comparisons among trauma intramedullary nails may not only be design dependent, but is also governed by the relationship between expected in vivo lifetime and stress level. The relationship between cycle count and predicted stress level is not universal, however, since the mechanical performance changes based upon the biomaterial chosen, and may do so during the timespan encompassed within the rehabilitative window.
Hartsell Z, Cartner J, Jones B, Ricci W	LOAD BEARING VERSUS LOAD SHARING: WHAT ROLES DO BONE AND IMPLANT PLAY DURING HEALING?	The purpose of this study was to evaluate strain distribution along the length of distal femur plates for different bone qualities, fracture patterns, and screw types. Eight groups of five specimens included: either a simulated healthy or osteoporotic bone surrogate, each with either a simple oblique fracture without a fracture gap (OTA 33A1) or a complex fracture with a 2 cm gap (OTA 33A3), and each with either locked or non-locked proximal fixation. Distal fixation was with locked screws in all specimens. Locking distal femur plates were instrumented with eight strain gauges at increasing distances from the fracture. Strain data was collected during quasi-static elastic loading. Loading was repeated 5 times per construct per group. In all instances plate strain was greatest near the fracture with both fracture types having similar qualitative trends. A3 fractures resulted in greater plate strain in all cases ($p < 0.05$). For non-osteoporotic A3 fractures, non-locked constructs had greater plate strain than locked constructs ($p < 0.05$). Conversely, locked constructs had greater plate strain in osteoporotic A3 specimens ($p = 0.001$). Regardless of bone quality, fracture pattern, or screw type, plate strain in distal femur fixation is concentrated near the fracture region. More complex fractures result in higher strain in the plate, indicating a lack of load sharing by bone. Both bone quality and screw type affected plate strain and must be considered in instances when working length constraints create high localized plate strain.
Dereje N. Abdi,Benjamin Walters, M Shah Jahan	Oxidation in UHMWPE Powder Containing Vitamin E: Combined TSL, ESR, and FTIR Analyses	Oxidative degradation of ultra-high molecular weight polyethylene (UHMWPE) due to gamma irradiation has been a major concern in total hip and knee joint arthroplasty. Irradiation (gamma or electron beam) is done for sterilization or crosslinking of UHMWPE. However, in the past decade the use of biocompatible stabilizer, alpha-tocopherol (vitamin E) has been introduced to reduce or eliminate radiation induced oxidation of UHMWPE. Most show limited or no oxidation in vitamin-E-containing UHMWPE, depending on concentration. While existing literature contains information comparing consolidated UHMWPE, we have studied the UHMWPE powder in an attempt to obtain a more basic under-standing of the activity in the unconsolidated material. GUR1050 powder, and the same powder containing 1000ppm vitamin E (provided by Ticona, Florence, KY), were irradiated (Steris, Libertyville, IL) to 30-kGy- gamma in both air and in nitrogen. We have then used electron spin resonance (ESR) to observe free radical behavior at multiple time periods after storage in air, and compared with similarly-timed thermo-luminescence (TSL) measurements, in an attempt to correlate the two sets of observations. Finally, FTIR testing was performed at the conclusion of the measurements (after 395 days in air) to obtain oxidation data, relative amongst the samples. The decay behavior of radicals as a function of time is obtained by double integration of the first derivative ESR spectrum and it suggest that, irrespective of the initial irradiation environment, there is a significant decay of free radicals in all of the samples; at the end of the 395 days all the samples shows a similar structure of ESR spectra.TSL results suggest that 1050-E shows a weak luminescence peak without gamma-irradiation and this peak (which is at peak shoulder near 185oC) has a much higher intensity in the irradiated samples. This peak is unaffected by the presence of air and may be attributed by the thermal breakdown of the vitamin-E radical. Hopefully these results will provide an additional information point to include among the existing literature concerning vitamin E in UHMWPE, enabling a more thorough understanding of its interactions.
James B. Bennett, Amanda L. Glover, David E. Nikles, Jacqueline A. Nikles, Christopher S. Brazel	Magnetic Heating of Fe3O4 Nanoparticles and Fe3O4-loaded Polymeric Micelles for Magnetothermally-Activated Drug Release	Magnetic nanoparticles, MNPs, combined with stimuli-responsive polymers show potential to improve cancer therapy via multifunctional nanoscale drug delivery systems. Our approach investigates the use of magnetite, Fe3O4, nanoparticles, which generate heat under an alternating current (AC) magnetic field, to stimulate the release of doxorubicin from an RGD-peptide targeted thermo-sensitive poly (ethylene glycol)-b-poly (caprolactone)(PEG-PCL) micelle. Fe3O4 nanoparticles synthesized in UA laboratories were exposed to magnetic fields of multiple frequencies, f, and field strengths, H, to characterize their ability to heat using a custom magnetic induction unit. The results showed magnetic heating of the MNPs could induce hyperthermic temperatures above the melting range of the micelle semi-crystalline poly (caprolactone) core. Specific absorption rates (SAR) for the Fe3O4 nanoparticles were in the range of previously reported magnetite SARs, and followed the relationship with magnetic field strength predicted by the Rosensweig equation. PEG-PCL micelles loaded with Fe3O4 nanoparticles exposed to the AC magnetic field also exhibited the ability to heat and potential for use in triggered drug release. Initial drug release studies using doxorubicin- loaded micelles show a temperature-dependent acceleration of drug release at temperatures above 42 ºC, the melting point of poly (caprolactone).

R. Trent Beatty and Christopher S. Brazel	Magnetic Melting-Activated Drug Delivery: Effect of Additives on Polycaprolactone Crystallinity and Melting Point	A micelle-based magnetically-triggered drug delivery system is under development, the core being comprised of polycaprolactone (PCL). The core of the micelle also contains magnetic nanoparticles and a drug. Additives and solvents that are used in preparing the micelles may also be present, such as oleic acid, triethyl amine, and dimethyl sulfoxide. This paper investigates the effect of each of these additives on the melting temperature and crystallinity of the PCL core. For all five additives there was no significant change in the melting temperature for PCL with MW = 2000 and only a one or two degree difference was observed in the melting temperature for PCL with MW = 1250. This effect is desired because the additives will not interfere with the amount of heating required to trigger drug release from the micelles. For PCL 2000 there was a slight increase in crystallinity with more additive. Increased additives to PCL 1250 showed an increase in crystallinity for most, yet some showed an increase and then decrease in crystallinity as more additive was introduced. A reduction in crystallinity is desired with addition of drug and nanoparticles, as the energy required to melt the micelle cores can be minimized.
Paul Bonvallet, Susan Bellis, Katie Culpepper, Matthew Phipps	Designing Electrospun Scaffolds for Skin Regeneration	Electrospinning is a technique in which a scaffold consisting of nanofibers resembling native human skin tissue is constructed. 30% polycaprolactone(PCL) and 70% collagen I were electrospun in a layer-by-layer fashion. Confocal images of DAPI stained fibroblasts expressing GFP were captured for visualizing the viability of cells. Scaffolds containing fibroblasts were grown in culture over 21 days to quantitate proliferation by assessing ATP and DNA quantities. The results showed the fibroblasts adopted a spread morphology typical of fibroblasts. Also, both ATP and DNA quantities had increased by more than 2-fold. We measured scaffold contraction and noticed significantly less contraction than current therapies used in clinic. Additionally, an in vitro full thickness skin model was constructed by seeding keratinocytes at an air-liquid interface on a scaffold containing embedded fibroblasts. Fluorescent stains BRDU, CK10, and DAPI were used to demonstrate this model forms a stratified epidermal layer upon. Finally, a PCL/collagen scaffold was constructed and implanted in a rat with a full thickness skin wound. Results show that implanted electrospun matrices recruit endogenous keratinocytes and assist in stratification of keratinocytes. The obtained results suggest these scaffolds are similar to native human dermal tissue and have high potential for accelerating the wound healing process.
Latisha Puckett,1,2 Raman Subramanian,1,2 Z. Ryan Tian1,2,3,4,5,6,7	Electrochemically Monitoring Electrolytes on Implantable TiO2/Ti Nanostructures	1Chemistry/Biochemistry, 2Institute of Nanoscience and Engineering, 3Biomedical Engineering, 4Cell/Molecular Biology, 5Microelectronics/Photonics, 6Electrical Engineering, 7Chemical Engineering, University of Arkansas, Fayetteville, AR 72701 The development of a facile mechanism for quantitatively monitoring tissue regeneration in real-time is a long-unmet challenge in clinical tissue regeneration research. On the implant even the electrolyte contents in body-fluid that can, in theory, serve as an indicator for indirectly quantifying tissue growth were seldom monitored systematically in, for instance, the bone-tissue regeneration. Many of the commonly used methods for monitoring tissue growth are far from being user-friendly for such real-time monitoring on, especially, patients. Thus, it would be a scientific advancement to develop a simple in vivo method that is ideal for real-time recording of tissue growth. Here we report a new miniaturized nanodevice that converts a nanostructured native oxide coating on the implantable titanium surface to a simple biosensor that is capable of electrochemically detecting changes in electrolyte concentrations near the implant surface. Using such a bone-implant as a working electrode, linear correlations between electrolyte concentrations and impedance-signals were established for the first time. Based on this discovery, sets of systematic studies for both in vitro and in vivo quantifications of bone-tissue growth are actively undergoing.
Michelle Fuentes	Skeletal Muscle Regeneration on Biodegradable Mesh for Hernia Repair	Incisional hernias are a common clinical problem occurring in up to 10% of all patients undergoing abdominal procedures. Currently prosthetic (both synthetic and biological) mesh is used for the repair. Despite these approaches, reoccurrence rates are reported to be 24%-54%. This is in part due to the fact that implanted mesh used for treatment leads to the restriction of abdominal wall mobility. Permanent implanted mesh pieces cause persistent inflammation and irregular scar formation. To address this problem this study proposes a technique that utilizes a biodegrading hernia mesh and impregnating it with cells to regenerate skeletal muscle in order to restore natural muscle function. Using the biodegrading mesh as a scaffold a thin layer of gelatin crosslinked with glutaraldehyde was added to create a temporary coating for which the cells can attach to and grow on. Initially the cells are allowed to proliferate in medium with 10% FBS until reaching approximately 60% confluency. Then the medium is switched to medium containing 2% horse serum, which stimulates myoblastic differentiation. Under these conditions, the cells form a multilayered network of myotubes. Through this technique skeletal muscle can be engineered to replace the biodegrading hernia mesh and potentially restore more natural function.
Benjamin Reves, Joel Bumgardner, Warren Haggard	Investigation of Chitosan-nano-hydroxyapatite beads and scaffolds for bone regeneration	Scaffolds for bone regeneration should display a number of characteristics including degradation that matches the rate of tissue ingrowth and mechanical properties similar to that of native bone. Previous composite chitosan-nano-hydroxyapatite scaffolds displayed good biocompatibility but slow degradation. The goal of this study was to fabricate scaffolds that had increased degradation while maintaining sufficient mechanical properties. Chitosan-nano-hydroxyapatite microspheres were fabricated using a co-precipitation method. Scaffolds were produced using a mild acid wash to make the beads adherent. The degradation and mechanical properties of microspheres and scaffolds were determined.
Orlandis Scott	Chitosan Calcium Phospate Membranes	Chitosan is a polysaccharide that is biodegradable and biocompatible. Chitosan may be electrospun into no-woven nano-fibrous mats for use as guided tissue membranes to help in bone regeneration and healing of adjacent soft tissue. A major disadvantage with using the chitosan nano-fibrous membranes is that they can be very weak and easily torn during handling by a surgeon. Calcium phosphate materials are commonly used as coatings on dental/orthopedic implants and in bone tissue engineering due to their chemical similarity to native bone mineral. The disadvantage with using calcium phosphate is that it's brittle and not flexible. By combining chitosan and calcium phosphate we may form a composite material with improved strength and toughness as well as with enhanced bone and tissue healing characteristics. In this project, we aim to deposit carbonated substitute calcium phosphate particles onto electrospun membranes to mimic the natural mineral-fibrous extracellular matrix of bone. The goal of this is to provide a more tissue like surface for the bone cells to regenerate bone and to increase strength of the guided tissue membrane.

Jason Brewer, Ben Walters, M.S. Jahan	Long-Term Effects of Storage Environments of Elevated Temperature of Free Radicals in UHMWPE	Ultra-high molecular weight polyethylene (UHMWPE) is often used as a component in hip and knee joint replacements. Gamma irradiation is often used for crosslinking or sterilization during the manufacture of these UHMWPE components. This irradiation creates free radicals in the material which may remain after manufacturing is complete (especially if it is gamma-sterilized). The formation of free radicals can increase the potential for, and extent of, oxidation of the UHMWPE and subsequent osteolysis - a primary reason for implant failure . Heat treatment, such as annealing, can be used to eliminate free radicals, but heat can compromise mechanical properties of the UHMWPE. Free radical content in the UHMWPE may also change over time. We have examined free radicals in UHMWPE when exposed to different temperatures (Room temperature, 35 degrees Celsius, and 75 degrees Celsius) and environments (air and inert) and have monitored them over long periods of time, up to 15 years. This may provide important information about the long-term effects of heat on free radicals in UHMWPE and their changes over time in different storage environments.
Tao Lowe, Linfeng Wu, Keegan Compton	Development of Hyaluronic Acid Hydrogels for Neural Tissue Regeneration	The purpose of this study is to design hyaluronic acid (HA) based hydrogels to differentiate neural stem cells for neural tissue regeneration. HA monomers are synthesized by conjugating 2-aminoethyl methacrylate (AEMA) to hyaluronic acid with different molecular weights. Macromer structure is characterized by ATR-FTIR and NMR and cytotoxicity by MTT assay. HA hydrogels are synthesized by photo-polymerization, mechanical properties studied by rheometer and DMA, and degradation characterized. PC-12 and neural stem cells are encapsulated in the hydrogels in situ during photo-polymerization and stained to determine cell viability. Differentiation of neural stem cells is induced by various growth factors. Efficiency of cell differentiation is still under investigation. ATR-FTIR and NMR measurements confirm successful synthesis of HA-AEMA macromers, whose substitution degree can be modulated by changing molecular weight of HA and ratio of AEMA to HA. MTT data indicates these macromers are not cytotoxic. Hydrogels can be formed under mild photo-polymerization conditions, and cell staining confirms cell viability in these conditions. Growth factor induced differentiation of ocular stem cells is currently under investigation. HA hydrogels have great potential for in situ encapsulation and differentiation of neural stem cells for neural tissue regeneration.
Jonathan M. Page, Edna M. Prieto, Jerald E. Dumas, Katarzyna J. Zienkiewicz, Joseph C. Wenke, Pamela Brown Baer, and Scott A. Guelcher	Reactivity and Biocompatibility of Injectable Polyurethane/Allograft Bone Biocomposites	Injectable and settable bone grafts offer significant advantages over pre-formed implants due to their ability to be administered using minimally invasive techniques. In this study, the effects of stoichiometry and catalyst concentration on the reactivity, injectability, and biocompatibility of two component lysine-derived polyurethane (PUR) biocomposites were investigated. Rate constants were measured for the system using an in situ ATR-FTIR technique, and a kinetic model predicting the conversion of the individual components was developed based on the measured rate constants. Despite the fact that TEDA is a well-known gelling catalyst, it was found to preferentially catalyze the blowing reaction with water relative to the gelling reactions by a ratio >17:1. Thus the kinetic model predicted that in the presence of water, the conversions of polyester were incomplete (<70%), which was in agreement with leaching experiments showing that only non-cytotoxic polyester and DPG were released from the reactive PUR. The PUR biocomposite supported cellular infiltration and remodeling in femoral condyle plug defects in rabbits at 8 weeks. Furthermore, there was no evidence of an adverse inflammatory response. This favorable combination of injectability, settability, biocompatibility, and osteoconductivity underscores the potential utility of lysine-derived polyurethane networks as injectable bone grafts.
Andrew J. Harmata, Edna M. Prieto, Katarzyna Zienkiewicz and Scott A. Guelcher	Effects of surface modification of 45S5 bioactive glass on bioactivity and mechanical properties of polymeric biocomposites	In tibial plateau fractures, calcium phosphate cements have proven to be superior to autograft, however their brittleness, low shear strength, and slow remodeling can result in prolonged recovery times, joint stiffness, and cost to society. Injectable polyurethane (PUR) biocomposites, specifically made with 45S5 bioactive glass (BG), are an attractive alternative due to their tough mechanical properties and active remodeling. We investigated the effects of BG surface modification (silane coupling agent 3-aminopropyl-trietoxysilane and surface grafting of polycaprolactone (PCL)) on the bioactivity and mechanical properties of PUR/BG composites. Based on an in vitro apatite-forming assay, the bioactivity of PCL-modified BG was slightly delayed compared to unmodified-BG. This delay is attributed to less active surface reaction sites available on the PUR-modified BG surface, as the PCL maintained on the surface throughout the assay. PUR composites incorporating unmodified-BG exhibited an ultimate yield strength and Young's modulus of 31.35 ± 1.30 MPa and 807.73 ± 6.12 MPa, compared to 67.37 ± 2.58 MPa and 3225.84 ± 255.93 MPa, respectively, for PCL-modified BG composites. Supported by work of adhesion measurements and calculations, this increase in strength is attributed to improved adhesion between the BG and PUR phases due to improved wettability as well as chain entanglements.
Anne D. Talley, Edna M. Prieto, Katarzyna J. Zienkiewicz, David T. Silliman, Pamela Brown-Baer, Joseph C. Wenke, Scott A. Guelcher	Injectable Polymer/β-TCP Biocomposite Delivery Systems for rhBMP-2	Growth factors incorporated into scaffolds for tissue engineering promote the infiltration of cells and tissue. Recombinant human bone morphogenetic growth factor-2 (rhBMP-2) stimulates osteoblast differentiation and new bone formation with localized delivery. Biodegradable polyurethane (PUR) biocomposites incorporating allograft bone particles have been reported to be effective carriers for rhBMP-2 and support new bone growth. β-Tricalcium phosphate (β-TCP) is a biocompatible, resorbable ceramic that has been used effectively as a substitute for allograft bone, bypassing biological and regulatory challenges associated with the combination of allograft bone and growth factors. We investigated the ability of an injectable PUR/β-TCP composite with rhBMP-2 to heal 8-mm critical-size calvarial bone defects in rats. Biocomposites were created with 45wt% β-TCP with and without 200 μg/mL rhBMP-2. Porosity of the scaffolds is important for the control of rhBMP-2 release and cellular infiltration. SEM images show that porosity of scaffolds cured in vivo compare to those cured in vitro. Faxitron images and μCT data suggest that PUR/β-TCP biocomposites support new bone formation and remodeling after 4 weeks in a rat calvarial defect model. Addition of rhBMP-2 to the biocomposite enhances new bone formation, which underscores the potential of these materials as a completely synthetic carrier for rhBMP-2.
Angela Zachman, Aidan Bo	Macrophage adhesion, activation, and apoptosis on biodegradable polyurethane scaffolds	A new class of polyurethane (PUR) materials has been designed to degrade by hydrolytic and oxidative mechanisms to control the inflammatory response. Surprisingly, these materials exhibited decreased water absorption and elastic modulus with increasing concentration of low molecular weight polyethylene glycol (PEG). To investigate the inflammatory response to these materials, human blood monocyte-derived macrophages were cultured on these PUR films. Macrophages preferentially adhered to phase separated PEG domains, correlating with increased protein adsorption on films with higher PEG content. Macrophages also showed increased levels of apoptosis with increased PEG content, while classical inflammatory activation signals, such as phagocytosis and superoxide production, decreased. To investigate whether the increased levels of apoptosis were due to increased cell-material adhesion or increased cell density on PEG domains, macrophages were cultured in high and low cell densities on both low adhesion silicon films and high adhesion gelatin-coated films. Although increased cell density did increase apoptosis to some extent, increased cell-material adhesion was found to more strongly promote apoptosis of macrophages. These findings indicate the importance of cell-material interactions in regulating inflammatory response to implanted biomaterials.

Brian C. Evans, Mukesh K. Gupta, Craig L. Duvall	Cell-permeant, pH-responsive Nano-carriers for Intracellular Peptide Delivery to Prevent Graft Failure	Intracellular delivery of a peptidic MAPKAP Kinase II inhibitor (MK2i) with a cell penetrating peptide (CPP) can reduce intimal hyperplasia (IH) in human saphenous vein grafts, however, the efficacy of this approach is limited due to intracellular trafficking for exocytosis or lysosomal degradation. To overcome this barrier, we have synthesized a series of cell-permeant, endosomolytic nano-carriers composed of varied molar ratios of 2 different amphiphilic polymers: a pH responsive copolymer reversibly conjugated to a MK2i-CPP fusion peptide and a poly(ethylene glycol) (PEG) terminated pH responsive diblock copolymer. Both diblock polymers contain the same pH-responsive, hydrophobic block that drives self-assembly into micelles at physiologic pH and disassembly/endosomal disruption at slightly endosomal pH. Two different compositions of the core-forming block with varied hydrophobicity have been synthesized for P1 and P2 to tune this assembly/disassembly behavior. The size and zeta potential were determined for each composition of the mixed micelles. pH-dependent activity was analyzed by monitoring micelle size at various pH values and endosomolytic activity analyzed through a hemolysis assay. Reducible conjugation of the fusion peptide was demonstrated with SDS-PAGE. We hypothesize that these nano-carriers will mediate efficient intracellular delivery of a therapeutic peptide to prevent IH and graft failure.
Yi Liang, Spencer W. Crowder, Andrew M. Park, Peter N. Pintauro, William H. Hofmeister, Lucas Hofmeister, Hak-Joon Sung	Electrospinning Carbon Nanotubes with Polymer to Improve Electroconductivity of Fiber Mesh Scaffolds for	Conductive polymer fiber scaffolds are an excellent tool to induce controlled cell differentiation in many applications such as promoting the differentiation of embryonic stem cells (ESCs) to cardiomyocytes. Fiber scaffolds mimic the structure of the extracellular matrix, providing a physiologically-relevant format for studying cell differentiation. Electrospinning is popular method for generating fiber scaffolds because it is inexpensive and highly tunable. Therefore, poly(ε-caprolactone) (PCL) was electrospun into fibers. PCL is biocompatible but it has a low electrical conductivity. To compensate for its low conductivity, multiwall carbon nanotubes (MWCNTs), known for their high electrical conductivity, were incorporated into the PCL solution prior to electrospinning to increasing the conductivity of the fibers. This scaffold can be developed into a cardiac patch to enhance cardiomyogenic differentiation of ESCs for cardiac tissue regeneration. Selection of solvents and loading of MWCNTs were optimized for scaffold fabrication. A 1:1 ratio of THF/DMF solvent generated smooth, consistent fibers. Surprisingly, fiber conductivity did not increase linearly with increasing concentration of MWNTs. A 3% w/w MWCNT/PCL concentration resulted in the highest electrical conductivity. Further cell studies are currently being conducted to investigate the properties of this fiber scaffold system on cardiomyogenic differentiation of ESCs.