Graduate Studies

Regenerative Medicine and Cell Biology

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

Regenerative Medicine & Cell Biology

http://regmed.musc.edu
Message from the Chair

Welcome to the Department of Regenerative Medicine and Cell Biology. The goal of the department is to apply our knowledge of molecular and cellular biology to understand and reverse human disease. Regenerative medicine is an emerging field that aims to revolutionize the treatment of disease by providing cures rather than treating symptoms. It relies on multidisciplinary approaches that require expertise in diverse areas. Approaches include the use of stem cells to provide limitless supplies of cells for transplant therapy and disease modeling, bioengineering and tissue engineering to generate replacement tissues and organs, and the production of transgenic animals to study the fundamental molecular basis of organ formation and disease. The department has active research programs in tissue fabrication and bioengineering, cardiovascular development and liver disease, cancer biology, cell signaling, and drug development. The department is also heavily involved in biomedical education through the training of medical and graduate students. We believe that our students are among the very best in the country and are the engine that accelerates scientific and clinical breakthroughs. Regenerative medicine is at a particularly exciting stage, with students and investigators being poised to make discipline-changing advances of high impact. The field is on the cusp of revolutionizing biomedical science, and as regenerative medicine researchers we are limited only by our imaginations.

Stephen A. Duncan, DPhil
Professor and Chair
SmartState Chair in Regenerative Medicine
Message from the Graduate Coordinator

Dear Prospective Students,

I am the graduate coordinator for the Department of Regenerative Medicine and Cell Biology at MUSC. Our group is internationally known for its work on various aspects of developmental biology, regeneration, and tissue engineering. Additionally, our department is designed to establish collaborative networks of excellence focused on developing new scientific insights into the mechanisms of cardiac, liver, and vascular diseases. In all areas of research, our faculty asks critical, clinically relevant questions that are then answered at the bench. We are a dynamic, integrated faculty that embraces the opportunity to train students. It is my job as graduate coordinator to introduce you to our department and make your transition to basic science research as seamless and enjoyable as it should be. Whatever your background or scientific interests, we as a department, would be excited for the opportunity to work with you and cultivate your innate scientific interests. I would be excited to tour you around the department and facilitate introduction to various faculty as well as go over brief introductions from each of the eligible faculty. I am at your service and would be excited to talk to you further about options in our department and at MUSC.

Russell “Chip” Norris, PhD
Department Graduate Studies Program Director
Regenerative Medicine and Cell Biology
Two broad disciplines are studied by faculty in the Regenerative Medicine and Cell Biology Department and are detailed below. Some of our faculty cross over these topic areas and are listed twice.

Developmental Biology with Links to Human Diseases

Developmental biology is a rich resource for clinicians who seek to understand the underpinnings of their patient’s disorders, to identify candidate interacting genes and in some cases, to discover therapies. Conversely, the burgeoning number of genes that are being identified based on human disease phenotypes is informing developmental biologists of unanticipated genetic connections and suggesting hypotheses about genetic and cell biological circuitry that can be tested in model organisms. As a goal, our group utilizes various approaches to identify how pathogenic mechanisms underlying disease phenotypes. Faculty listed below focus on biological aspects of diverse human conditions including cardiac diseases, angiogenesis/vascular diseases, diabetes and cancer.

**Stephen Duncan, DPhil** [duncanst@musc.edu]

Research in the Duncan laboratory focuses on liver development and disease using mice and induced pluripotent stem cells (iPSCs) as model systems. The liver, in which 80% of the cells are hepatocytes, offers an attractive and relatively simple system in which to study the role of transcription factors during morphogenesis and development.

In the laboratory, we use transgenic and knockout mice and genetically modified iPSCs to uncover the mechanisms through which transcription factors and cell signaling molecules are required to drive liver development.

**Roger Markwald, PhD** [markwald@musc.edu]

My laboratory has pursued studies on the cell and molecular mechanisms of heart development that utilized in vivo dynamic labeling studies to demonstrate that heart development is progressive, irreversible and occurs by the addition of new segments including ones derived from extracardiac sources. Current studies focus on using patient based, gene discoveries for developing remedial etiologies and therapies for congenital heart malformations and developmentally-linked, adult heart valve diseases.
Andy Wessels, PhD [wesselsa@musc.edu]
The overall goal of the research performed in the Wessels Laboratory is to unravel the developmental events that are involved in normal cardiac development and to elucidate the mechanisms that lead to congenital heart malformations. The lab currently focusses on two major research projects related to this theme: elucidating the role of the dorsal mesenchymal protrusion (DMP) in the pathogenesis of Atrioventricular Septal Defects (AVSD), and establishing the role of epicardially-derived cells (EPDCs) in valvuloseptal development.

Martin Morad, PhD [moradm@musc.edu]
Dr. Morad is an internationally recognized scientist in the field of cardiac electrophysiology and calcium signaling, specifically in the area of calcium-binding proteins. The cardiac muscle is a complex system composed of 40,000 proteins. These proteins “tell” the heart how to contract and how fast; they also control how heart muscle grows and regenerates. Calcium acts as a signaling mechanism in the function of these proteins. Dr. Morad seeks to discover what causes these calcium signaling mechanisms to stop working properly, which can result in congestive heart failure. Understanding this process could lead to new therapeutic approaches to treat congestive heart failure and other conditions, and to the world’s first tissue-derived human heart pacemaker.

Robin Muise-Helmericks, PhD [musehelm@musc.edu]
Our laboratory focuses on the molecular regulation of angiogenesis by the Akt family of kinases. We are particularly interested in the role of these kinases during angiogenesis as they pertain to metabolism, development and cutaneous wound healing. Our work can be divided into two major subject areas: mitochondrial homeostasis and angiogenesis, and tissue regeneration using a marine derived nanofiber.
Chip Norris, PhD [norrisra@musc.edu]

A primary focus of the Norris lab is to deal with basic questions in formation of the cardiac valves and pathological processes that result in valve disease. The overall design follows a “cycle of discovery” that begins with the clinical condition, identifies gene candidates, and explores their mechanism of action. These mechanistic studies, in turn, point to related pathways for further gene discovery. Through an international consortium of clinicians and scientists, our group has identified genetic and biological causes for common cardiac disease, e.g. mitral valve prolapse and bicuspid aortic valve disease. Our ongoing projects have defined that these genes play a crucial role during the development of the valves, essentially laying the blueprint for valve construction. Thus, inherited heart valve disease is caused by inborn errors in the development of this structure. By studying these disease genes we can gain an understanding for how the valve develops and why valve defects occur. Harnessed with this information, targeted therapeutics can be developed that may be of benefit to patients with valvular heart disease, thus allowing us to complete the “cycle of discovery”.

Christi Kern, PhD [kernc@musc.edu]

I am interested in the extracellular matrix (ECM) i.e. the proteins and molecules that make up the outside environment of cells. In adult tissues the ECM is often referred to as connective tissue since it serves to connect different tissue types together and provides a framework of support to organs. The specific class of ECM molecules that we are focused on is the proteoglycans; protein cores that are decorated with sugar moieties and that are also subject to proteolytic cleavage. The fact that the ECM is dynamic during development, wound healing and disease, is an aspect that is particularly interesting to my lab, and one where relatively few researchers are focused. Although my initial area of interest has been cardiovascular development and disease my group has recently expanded our research focus to include studies that investigate the development of temporomandibular joint.
Yukiko Sugi, DVM, PhD [sugiy@musc.edu]

Research in the Sugi laboratory focuses on cardiac development using genetically engineered mouse models, primary cell cultures and in ovo whole chick embryo cultures with cellular and molecular biological approaches. The current research focus of the Sugi laboratory is endocardial cushion remodeling and prevallular fibroblast differentiation that are critical developmental events for four-chambered heart formation and valvuloseptal morphogenesis.

Kyu-Ho Lee, MD, PhD [leekh@musc.edu]

The Lee Laboratory, in the Departments of Pediatrics at MUSC Children’s Hospital, investigates two major disease areas affecting child and maternal health: Congenital heart disease (CHD), which affects approximately 1% of live births; and preeclampsia or hypertension in pregnancy, which occurs in 3-5% of pregnancies. These efforts revolve around the genetic pathways leading to and emanating from the early cardiac transcription factor, Nkx2-5. Missense sequence variants of Nkx2-5 are associated with about 4% of human CHD, and altered Nkx2-5 expression levels in experimental mice has a profound effect on development of the Second Heart Field (SHF), a distinct set of heart precursors which gives rise to outflow tract (OFT), right ventricle and atrial septal regions of the developing heart.

Michael Kern, PhD [kernmj@musc.edu]

Research in my laboratory is currently focused on the carboxyl terminal region of the Prrx proteins which contains an OAR domain. In total there are 16 human proteins that contain a version of the OAR domain. Although it is phylogenetically conserved through Drosophila, not much is known about this domain in any specie. Work in our laboratory and others has led to the hypothesis that the OAR domain is a cofactor binding site, and that protein-protein interactions between the 16 OAR containing proteins and an unknown suite of cofactors likely modulate transcription of nearby genes. My current research is focused on identifying these OAR cofactors, their specificity for the 16 OAR domains, and how these interactions modulate transcriptional
regulation. This work is critical since all 16 OAR containing proteins are integral to morphogenesis of many tissues and organs. In addition, our collaborative work has demonstrated that Prrx1 is linked to diabetes, therefore highlighting an additional role for these important homeodomain proteins.

Rick Visconti, PhD [visconrp@musc.edu]

Certain organs, such as the heart, lack inherent mechanisms for functional recovery after injury. With this in mind, the overall research focus in the Visconti lab is on elucidation of the cellular and molecular mechanisms through which endogenous stem cell populations contribute to both the embryonic morphogenesis of cardiovascular tissues and to their pathological remodeling following injury or disease. Our belief is that a fundamental understanding of how stem cells contribute to these natural functions will provide insights that can be applied to regenerative interventions. Our lab currently focuses on two projects related to this theme: (1) elucidation of the contribution of hematopoietic stem cells to cardiac morphogenesis during embryonic development and to pathological remodeling of the heart in disease; and (2) acceleration of the assembly and maturation of small diameter bioengineered vascular grafts by improving heterotypic vascular cell interactions.

Samar Hammad, PhD [hammadsm@musc.edu]

The main focus of the Hammad laboratory has been on sphingolipid signaling mechanisms which mediate the survival of foam cells (lipid-laden macrophages) and their sustained cell activation in response to modified lipoproteins and lipoprotein-immune complexes. The transformation of macrophages into foam cells is a critical event in the development of atherosclerosis and defining mechanisms mediating foam cell formation and determining the role of foam cells in the pathology of atherosclerosis is an area of great clinical relevance. Our goal is to uncover targets in the signaling pathway such as receptors and/or sphingolipids that can have therapeutic implications for blocking cytokine release and prevention of vulnerable atherosclerotic plaques.
The extracellular matrix (ECM) is a three-dimensional network of molecules that surrounds cells in tissues and can direct organ morphogenesis, tissue repair and disease progression. Cells receive information from the ECM by means of cell surface receptors. This information is then transmitted from the ECM-cell interface by signaling pathways to elicit cellular behaviors such as migration, proliferation and differentiation. My major research emphasis is to understand how this network of molecules stimulates specific cellular behaviors. In our research we use both mouse genetic models and cell-based assays to study the role of the ECM in: Bmp-2-mediated bone formation and bone repair; Pericyte adhesion to vascular networks; and Cardiac development.

Targeting endothelial barrier dysfunction with HDL-S1P therapeutics:

Thus far, attempts at therapeutic elevation of HDL have not proved useful in reducing cardiovascular disease (CVD) risk in humans, despite evidence from epidemiological studies indicating that high levels of HDL cholesterol (HDL-C) inversely associate with risk for CVD. Findings from the laboratory of Dr. Kelley Argraves indicate that compositional differences of sphingolipids carried by HDL are related to the occurrence of ischemic heart disease (IHD), and suggest that these differences may contribute to the putative protective role of HDL in IHD and other vascular disorders.

Molecular mechanisms of the regulation of chemo resistance in colon cancer by Hyaluronan receptor CD44v6 (HyaR) signaling.


Regulation of receptor tyrosine kinases (RTKs that act as co-receptor to HyaR) downstream ant-apoptosis signaling by HyaR-signaling complex.
- Mechanisms of HyaR-regulated TGFβ1-induced NADPH Oxidase/reactive oxygen species (ROS) in skin sclerosis and lung fibrosis.
- Mechanisms of matricellular protein (Periostin and CCN1)-mediated mitral valve development pathways by Hyaluronan-CD44 signaling.

Shibnath Ghatak, PhD [ghatak@musc.edu]

Our current interests are in the bladder cancer where HyaR is overexpressed and in overactive bladder / interstitial cystitis where loss of glycosaminoglycan (hyaluronan) layer is one of the causes. Interaction of hyaluronan and HyaR in the bladder cancer cell is interrupted by using urothelium specific cre plasmid and the conditionally silenced shRNA plasmid as above. This loss hyaluronan can be rescued in overactive bladder / interstitial cystitis by transfecting hyaluronan synthase gene into the urothelium cell layer. In this case a mixture of floxed plasmid containing hyaluronan synthase gene and urothelium specific cre will be used.

Antonis Kourtidis, PhD [kourtidi@musc.edu]

The main focus of the Kourtidis lab is to fully understand the novel interaction of the adherens junctions (AJs) with the RNA interference (RNAi) machinery, as well as with other RNA-associated complexes. Our data obtained by confocal microscopy of fully polarized epithelial monolayers and high-throughput systems biology approaches, such as proteomics, miRNA arrays, RNA-CLIP, qPCR arrays, and next generation sequencing, reveal that the interaction of the AJs with RNA complexes, mRNAs, and miRNAs is extensive. This suggests that there is broad regulation of gene expression by the AJs at the post-transcriptional level. Elucidating all the modes and details of this mechanism and its role in regulating cell behavior is the main goal of our research.
The Wang lab focuses on pancreatic islet cell biology and transplantation immunology in the treatment of type 1 and type 2 diabetes and chronic pancreatitis.

The areas of investigation in the Wang lab include:

- Generation of insulin-secreting cells from adipose stem cells to expand the source of transplanted islets;
- Mechanisms that lead to islet death after allogeneic and autologous islet transplantation;
- Interventional approaches that can protect islets from apoptosis and immune rejection by induction of protective genes or encapsulating islets with nanoparticles;
- The role of HO-1 in obesity and insulin resistance;
- A translational approach that can prevent the onset of surgical diabetes after total pancreatectomy and islet autotransplantation for patients with chronic pancreatitis.
Bioengineering and Translational Medicine

Members of our group also focus on the fundamental ways chemical and biological engineering approaches drive and provide innovative technologies and solutions that impact clinical practice and/or commercial healthcare products. Our department sustains a long standing collaboration with Clemson Engineering. Faculty in our department are at the cutting edge of bioengineering sciences and are highlighted below:

Mike Yost, PhD [yostm@musc.edu]

Our research addresses the problem of muscle regeneration by combining modulation of inflammatory processes with tissue engineering-based regeneration strategies. The overall goal is to seamlessly regenerate fascicular segments of skeletal muscle.

Martin Morad, PhD [moradm@musc.edu]

Dr. Morad is an internationally recognized scientist in the field of cardiac electrophysiology and calcium signaling, specifically in the area of calcium-binding proteins. The cardiac muscle is a complex system composed of 40,000 proteins. These proteins “tell” the heart how to contract and how fast; they also control how heart muscle grows and regenerates. Calcium acts as a signaling mechanism in the function of these proteins. Dr. Morad seeks to discover what causes these calcium signaling mechanisms to stop working properly, which can result in congestive heart failure. Understanding this process could lead to new therapeutic approaches to treat congestive heart failure and other conditions, and to the world’s first tissue-derived human heart pacemaker.
Calcium ions play critical roles in intracellular signaling of a variety of cells. In cardiac and skeletal muscle, transiently elevated Ca\(^{2+}\) concentrations during muscle action potentials initiate muscle contraction. In my laboratory we are studying how these Ca\(^{2+}\) transients are well regulated and how aberrant intracellular calcium homeostasis causes diseases in the cardiac and skeletal muscle.

Research in my lab has been focused on screening peptide-functionalized synthetic hydrogel combinatorial microarrays, which can enable the rapid identification of “hit” materials with high binding affinity for cell surface receptors. This would allow for the development of materials-directed stem cell fate commitment as well as the next generation of tissue-engineering scaffolds. We are also involved in the development of bioinks capable of promoting microvasculature formation, and use them to fabricate pre-vascularized tissue engineering constructs. Our lab pioneered the utilization of silicon-based nanomaterials to facilitate functional assembly of hIPSC-derived cardiomyocytes to prepare human cardiac spheroids (3D spherical micro-tissues) for tissue engineering and drug testing applications.
Regenerative Medicine and Cell Biology Research Core Facilities

These facilities located in the Regenerative Medicine and Cell Biology department are shared resources which offer a wide range of services to the department and MUSC community, including cutting edge technologies, high end instrumentation, technical support, and education. Our facilities are committed to enhancing and expanding the collaborative capabilities of student and faculty research at MUSC.

Our core directors and lab personnel are highly trained experts in their field who provide technical expertise, consultation, and training. The cores available through our department are listed below:

**Morphology, Imaging and Instrumentation Core**

Thomas Trusk, PhD, Director, Josh Spruill Imaging Facility  
Andy Wessels, PhD, Director, Histology Facility

http://mmi.musc.edu

The Morphology, Imaging and Instrumentation Core provides the facilities, supervision, and training for histological methods and advanced imaging technology. This core builds on research investments from NIH/NCRR Shared Instrumentation Grants, NIH/NCRR COBRE programs, and an NSF Research Infrastructure Improvement Award. We provide skilled personnel capable of performing and training users in highly specialized techniques, such as confocal imaging, 3D reconstruction, immunohistochemistry, and *in situ* hybridization. Faculty and student investigators have access to core facilities to process tissue and operate the histological tools, microscopes, and analysis computers, and are assisted by core staff concerning experimental design, data interpretation and technical information to best utilize facilities and instrumentation. The Core has a 20-year record of providing state-of-the-art service and training to investigators at MUSC and throughout South Carolina. Core staff participates in a weeklong training workshop on confocal microscopy and has strong interactions with imaging cores at Clemson and USC in Columbia.

**Gene Function Core**

Michael Kern, PhD, Director

https://sctrweb2.musc.edu/cores_facilities/step/1/sub_step/98

The purpose of this core is to provide intellectual and physical resources for testing Gene Function to understand cardiovascular malformations and adult cardiac disease using transgenic mice, gene targeted mice, and viral vectors. Toward this goal the core has the following four main services (1) generate transgenic mice,
(2) generate gene targeted mice, (3) generate viral vectors to facilitate loss of function and gain of function analysis in cell culture and in vivo, (4) mentor the trainees in utilizing these techniques for cardiovascular research. There are two additional areas (plasmid construction and related mouse services) which support the main services described above. Without this core facility the research tools and technology of transgenic and gene targeted mice, as well as viral vector preparation and use, would be out of reach of most junior faculty. For them to invest in the training, or cost, to establish the technical resources and expertise, would come at the expense of focusing on their aims. This core will alleviate these issues and facilitate the analysis of Gene Function by the COBRE trainees and others at MUSC and the State of South Carolina.

Flow Cytometry Facility
Richard Visconti, PhD, Director
B. Jacob Kendrick, Facility Manager
http://regmed.musc.edu/flowcytometry

The Flow Cytometry Facility provides resources for performing a large variety of flow cytometry services using Beckman Coulter instrumentation. Current platforms include the new MoFlo Astrios for cell sorting applications and a CyAn ADP desktop analyzer for cell analysis. Facility personnel have considerable experience in high-speed, rare-event cell sorting and will be pleased to work with individual investigators to adapt or develop techniques to meet their specific research program.

Advanced Tissue Biofabrication Center
Waleed Twal, PhD, Director
http://regmed.musc.edu/atbc

The Advanced Tissue Biofabrication Center (ATBC) is a fully equipped laboratory intended for experimentation on building tissues and organs. The facility has 2 full tissue culture rooms for cell propagation. The center has one of a kind bioprinter designed by MUSC engineers and scientists capable of printing tissues in three dimensions. The center is also equipped with very sensitive testing equipment for tissues fabricated in the facility (e.g tensile strength and compression capability). The center also has a fully automated liquid handling unit for a variety of experimental procedures. The facility hosts a Luminex-type multiplex array reader capable of reading up to 100 different biological molecules from a small sample of fluids or cell culture media. The center also has the machinery needed for testing binding kinetics of biological molecules in real time using surface plasmon resonance technology.