OCASCR Research Grant Abstracts

(in reverse order by date)

Start Date	PI Last Name	Title	Abstract
01/01/2023	Audrey Cleuren, Ph.D.	Characterizing the inflammation-mediated reciprocal interaction between adipocyte and endothelial cell dysfunction in diet-induced obesity	Eating too much can lead to extensive weight gain called obesity. Obese people have a higher risk of getting heart diseases and diabetes. Although we do not know exactly how this works, it is known that it involves interactions between fat cells and cells that form the inner lining of blood vessels, called endothelial cells (ECs). One way these cells are believed to interact with each other is through inflammation, but so far it has been difficult to study this in detail. We will use special mice that allow us to look specifically at ECs so we can tell how they contribute to the health problems seen in obese people. For our studies we will focus on 2 different aspects of ECs: EC dysfunction and the ability of ECs to make new blood vessels. If ECs do not work as they should, they can promote inflammation that negatively impacts other surrounding cells. ECs are also important in making sure all cells in the body are in contact with the blood to get oxygen and nutrients. When cells are not in direct contact with ECs, they can die. Normally when the number of cells increases, ECs will form new blood vessels to supply the new cells. However, obesity can impair this process. Both these EC problems can lead to heart disease. By studying these processes in more detail, we hope to find ways to interfere with these problems. This could eventually help with finding better treatment for obesity and obesity-related diseases.
01/01/2023	Catherine Hunter, MD	Defining the role of the intestinal barrier in necrotizing enterocolitis using human enteroids	In this application we propose generating enteroids (mini-intestinal units) from human stem cells collected from infants with and without necrotizing enterocolitis (NEC). We describe a series of novel experiments to test these enteroids (control compared to NEC) for susceptibility to NEC-triggers. In early findings from our laboratory, we have found that the enteroids from babies who have had NEC are more easily inflamed and have a stronger response to NEC-triggers even after recovery. In this project we will define whether enteroids generated from patients with NEC are intrinsically more likely to have a severe response to NEC-triggers. We will build on this work to identify when some infants are more susceptible to NEC than others. The use of intestinal enteroids from human subjects will provide tremendous translational power and allow us to gain insight into the molecular, cellular, and organ-level determinants of NEC. The goal of this project is to gain insight into why some babies get NEC and identify targets for therapeutic intervention using an enteroid model generated from human stem cells.
01/01/2023	Chi Fung Lee, Ph.D.	Roles of mitochondrial dysfunction and NAD redox imbalance in obesity-induced arrhythmogenesis	Unhealthy diet (diet with high-fat, sugar, salt) and/or smoking cause obesity, diabetes, and high blood pressure, all of which are risk factors for cardiovascular disease. People with these risk factors have higher chances of heart disease. Mitochondrial malfunction is a hallmark of manifestations of heart disease. ~25% of the heart disease-related deaths result from the generation of irregular heartbeats. In addition, stem cell/regenerative therapies to hearts are known to induce irregular heartbeats but underlying mechanisms are largely unknown. Irregular heartbeats can induce sudden cardiac death, which has no cure. This study aims to understand how mitochondrial malfunction causes irregular heartbeat-related death and to provide insights into lowering risks for patients with obesity or after stem cell/regenerative therapies. Our group has the expertise and necessary tools to study mitochondrial metabolism and heart function. This proposal will allow us to explore a new venue to combat the deadly disease and generate data to compete for federal funding. We will further investigate the therapeutic potential by targeting mitochondrial dysfunction for irregular heartbeats in our next proposal submitted to the NIH.

01/01/2023	Raju V.S. Rajala, Ph.D.	Targeting cell cycle regulators in the retina as a therapeutic for neuroregeneration	The retina is a thin film in the eye that lets us see objects. It is composed of several neurons (nerve cells that send and receive electrical signals) that cannot regrow if they are lost. In several retinal diseases, these neurons die, causing blindness. Risk factors such as smoking, environmental, and genetic stress prompt the production of non-functional proteins that result in retinal diseases. Photoreceptors are a type of retinal cell that absorbs light and processes images through coordination with other retinal cells. Müller cells are supporting cells that can convert into any other retinal cells if we provide suitable conditions. Our laboratory has found that cell division control 2-like (Clk1), an enzyme, modifies protein function as one cell divides into two new cells and is present at higher levels in photoreceptor and Müller glial cells. The purpose of this grant is to study how Clk1 works with photoreceptors and Müller cells in replacing the dead neurons in retinal diseases. Vision loss affects millions of people each year. Current treatments only delay vision loss: they do not prevent it. Our goal is to preserve vision through neuron regeneration to replace dying retinal cells in retinal diseases.
07/01/2022	Alberola	Regulation of ILC development from hematopoietic stem cells	Innate lymphoid cells (ILCs) are a heterogeneous group of cells that live in barrier organs, such as the lung, the skin, the intestinal lining. They are very important in responding to pathogens and in regulating tissue repair after injury, such as influenza infections. If misregulated they contribute to disease, as in fibrosis, or COPD. This project is focused in understanding how these cells are generated from a hematopoietic stem cell progenitor, the common lymphocyte precursor (CLP) using mice deficient for a regulatory molecule c-Myb. These mice have a defect in the generation of ILCs, but we don't understand what aspect of their development c-Myb controls.
07/01/2022	Gorbsky	Mechanisms of aneuploidy surge in induced pluripotent stem cells	Induced pluripotent stem cells (iPSCs) are remarkably useful reagents for investigating the biology of cell growth, differentiation, and aging. Medically, they also offer tremendous potential for replacing damaged or aging tissues. With iPSCs a patient's own normal cells are reprogrammed to become stem cells. They can be reintroduced into the body where they repair damaged tissues. Normally when cells or tissues are used for transplantation, the immune system must be suppressed. Because iPSCs are derived from the cells of the patient, immune rejection does not occur. However, whether used for research or medicine, iPSCs must be grown for many generations in artificial culture. Unfortunately, the growth of iPSCs in culture often results in changes to the DNA of the chromosomes, limiting usefulness for research and potentially endangering patient health when used medically. Conventionally, chromosome abnormalities were thought to be caused by a single aberrant cell that grows faster and overgrows the normal cells after many generations. Our initial data suggest that this model is inaccurate and requires major revision. In the first few months of OCASCR funding of this study we have made significant progress on our initial aims designed to test the validity of our hypotheses. Our data indicate that chromosome abnormalities arise by an entirely novel mechanism that we will define. Here we request funding for a second year to complete these initial studies that will explore mechanisms for this entirely unprecedented chromosome behavior and generate data for submission of a grant application to the National Institutes of Health.
07/01/2022	Sathyaseelan	Role of hepatocyte necroptosis in obesity induced NASH	Obesity is a major risk factor for the development of nonalcoholic fatty liver disease (NAFLD), a spectrum of chronic liver diseases ranging from simple fatty liver to more severe nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC). Nearly 25% of people with fatty liver develop NASH, which is the second leading cause of liver transplantation in the United States and is a major risk factor for the development of HCC and cardiovascular disease. Currently, no treatments are available for NASH as we lack a clear understanding of the cellular and molecular mechanisms driving the progression of fatty liver to NASH. Studies have identified that chronic liver inflammation play a key role in the initiation and progression of NAFLD, however, pathways that drive chronic liver inflammation in NASH is not known. Necroptosis (a form of regulated cell death that causes inflammation) is reported to be activated in the livers of patients with NASH and inhibiting

			necroptosis reduces chronic liver inflammation in mouse models of NASH. The liver has many different cell types and of these the major cell type, hepatocyte, undergo necroptosis in obesity. In this proposal, we will test whether necroptosis specifically in hepatocytes contribute to chronic liver inflammation in obesity. The study will also identify the mechanism by which hepatocyte necroptosis activate liver immune cells (macrophages) to mediate inflammation. The data generated from this project will identify whether hepatocyte necroptosis-mediated inflammation drives the progression of fatty liver to NASH in obesity.
07/01/2022	Tsiokas	Integration of cellular signaling in skeletal stem cell differentiation	Adult bone marrow is a soft, spongy tissue residing inside the bones. It houses a type of stem cells called skeletal stem cells (SSCs) that can give rise to osteoblasts (bone forming cells), adipocytes (fat cells), and chondrocytes (cartilage). SSCs are made throughout adult life and are used to regenerate bones, fat tissue, and muscle, when needed. Defects in SSC differentiation can have widespread effects ranging from osteoporosis and chondrodysplasias to obesity and cancer metastasis. An outstanding question is how SSCs are pre-committed to specific lineages that give rise to mature osteoblasts, adipocytes, or chondrocytes, among other cell types. We approached this question by inducing a form of proteome reprogramming by deleting the gene encoding FBW7, an E3 ubiquitin ligase that targets for degradation numerous proteins of diverse functions and cellular roles. Going after the specific proteins affected by the deletion of FBW7, we identified two sets of proteins that influenced osteoblast differentiation. One set contained essential proteins for the formation and function of a cellular organelle called primary cilium. The second set of proteins included components of a large nuclear complex called the Mediator co-activator complex. In this proposal, we will examine whether and how these two sets of proteins communicate with each other to support osteoblast differentiation. Successful completion of our studies will have a significant impact on understanding mechanisms of chondrodysplasias associated with inadequate ciliary signaling and osteopenia in aging, associated with a reduction in bone mass and an increase in bone adiposity. They will also be impactful on tissue regeneration projects
07/01/2022	Unnikrishnan	Short-term dietary restriction rescues the age-related decline in intestinal stem cell regenerative capacity	Dietary Restriction (DR) is the most consistent intervention to-date shown to slow aging and increase lifespan. DR has also been shown to improve stem cell function in various tissues including intestinal stem cells (ISCs), enhancing its capacity to regenerate an entire intestinal tissue. In our first application we proposed that DR improves ISC function and prevents loss of ISC function that occurs with age. Over the past one year, we have established that DR implemented for short period can prevent the decline in ISC function that occurs with age and are characterizing the ISC population further. An additional year of support is requested to study the mechanism behind DR's effect on ISC function. It has been shown that stem cell function can be regulated by specific modifications in DNA such as DNA methylation. Therefore, we propose that DR implemented only for a short-period leads to changes in DNA methylation in the ISCs leading to improved function. We will measure DNA methylation in the whole genome of ISC obtained from young and old mice fed DR diet. First, we will identify the DNA methylation changes induced by DR and if these changes persists even if DR is discontinued. Second, we will identify genes associated to ISC function that can be regulated by DNA methylation changes induced by DR.
07/01/2022	Xia	Transplantation of proximal colon stem cell for regenerating the mucus barrier in the pouchitis mouse model	Inside a healthy person's large intestine, mucus forms a protective layer lining that protects the gut's surface from harmful gut bacteria. A defective mucus lining can cause inflammatory bowel disease (IBD), such as ulcerative colitis (UC). IBD affects ~1.3% of US adults, and many patients with severe disease require surgery to remove the diseased large intestine. However, sometimes after surgery, a complication related to inflammation, called "pouchitis", is common. We found that a lack of mucus protection contributes to this complication. We hypothesize that regenerating the defective mucus in the gut may be an effective treatment for pouchitis, and we propose to test this idea in mice. Intestinal stem cells (ISCs) can develop into various kinds of intestinal cells including those that make mucus. We previously discovered that mucus is primarily produced in the "proximal" area of

			the large intestine. Therefore, we will attempt to regenerate healthy mucus by transplanting proximal colon ISCs into mice who have a diseased intestine that is similar to pouchitis conditions in humans. We will determine whether and how the transplantation improves the inflammation of these mice. Our study will provide new insights into the potential of regenerating mucus-producing function as a treatment for patients with IBD. The knowledge gained from this study may be valuable for the research on what is known as regenerative medicine.
01/01/2022	Chiao	Mitochondrial oxidative stress in heart failure with preserved ejection fraction	Heart failure (HF) with preserved ejection fraction (HFpEF) is an emerging health problem with high morbidity and mortality. Unfortunately, there are presently no effective treatments for HFpEF. HFpEF is highly prevalent in older adults and is the leading cause of hospitalization in the elderly. About 80% of HFpEF patients are overweight or obese and obesity is a strong risk factor for HFpEF. However, it is unclear how aging and obesity make people more susceptible to HFpEF development. Obesity and aging are both associated with increased mitochondrial oxidative stress and oxidative damage in the heart. As adult heart muscle cells have little regenerative power, the heart is highly sensitive to oxidative damage. Our previous publication has previously showed that interventions reducing mitochondrial oxidative stress reverses pre-existing cardiac impairments and restores heart function in old mice. In this proposal, we will test whether increased mitochondrial oxidative stress predisposes the heart to HFpEF development and determine if intervention suppressing mitochondrial oxidative stress can rejuvenate the heart and reverse HFpEF symptoms. This study will provide crucial insights into the causal role of mitochondrial oxidative stress in HFpEF development. The results will provide a solid foundation for a future R01 grant to further investigate the mechanism by which mitochondrial oxidative stress impairs heart muscle cell function during HFpEF development and the therapeutic potentials of intervention targeting aging and obesity-induced mitochondrial oxidative stress to restore heart function in HFpEF patients.
01/01/2022	Frazer	Normal and malignant lymphoblastic stem cells	The ‘stem cells’ that make healthy—and cancerous—blood cells are poorly understood. These cells matter, because healthy ones grow new blood cells over our entire lifetime, while cancerous ones cause leukemias. Thus, learning about ‘good’ and ‘bad’ blood stem cells can reveal ways to grow healthy blood faster, and to kill leukemias using less-toxic medicines. We study zebrafish blood stem cells, because zebrafish blood is similar to humans, and we can genetically modify zebrafish easily. Exploiting this, we have built fish where one blood cell type (called B-cells) glows green, and another type (T-cells) glows red. We also built fish that develop B and T cell leukemias, which appear as either green or red tumors. In these leukemias, we find rare cells that are both green and red, which means these cells haven’t ‘chosen’ which type of cell to be—a feature of stem cells. In fact, we can even find rare green + red cells in normal fish that don’t develop leukemia. This project studies these scarce green + red cells, which we believe are blood stem cells. To test this, we will define the active genes in these cells (both normal and cancerous). We will also see what they are capable of, in two ways: (1) We will test if healthy green + red cells re-grow B and T cells in fish lacking them. (2) We will test if cancerous red + green cells grow B and T cell leukemias when transplanted into healthy fish.
01/01/2022	Hunter	Defining the role of the intestinal barrier in necrotizing enterocolitis using human enteroids	Necrotizing enterocolitis (NEC) is a deadly disease of the newborn, and affects 5-7% of babies in neonatal intensive care units. Prematurity and an abnormal response to bacteria in the gastrointestinal tract contributes to NEC. A strong intestinal barrier is the first line of defense against infection from the external world. In this application we propose generating enteroids (mini intestinal units) from human stem cells collected from infants and older patients. We describe a series of novel experiments to test these enteroids for susceptibility to NEC, by treating them factors recognized to trigger NEC. We will determine the effect of these triggers on the gut barrier and measure inflammation. We anticipate that the stem cell-derived human intestinal enteroid model of NEC will demonstrate a decrease in normal barrier function, and that strengthening this barrier will be protective against NEC. The use of intestinal enteroids from human subjects will provide tremendous translational power and allow us to gain insight into the molecular, cellular, and organ-level

			determinants of NEC. The goal of this project is to gain insight into why some babies get NEC and identify targets for therapeutic intervention using an enteroid model generated from human stem cells
01/01/2022	Janknecht	JMJD5 and testicular stem cells	Sperm is continuously produced from spermatogonial stem cells after puberty. However, up to 10% of males in the US are infertile, which can be due to defects in their spermatogonial stem cells. We found one protein, JMJD5, which may be required for the function of these stem cells and thereby male fertility. Notably, testicular tumors are very similar to spermatogonial stem cells and JMJD5 may also stimulate the growth of these malignancies. Here, we will elucidate with cell culture, tissue regeneration and mouse models how JMJD5 affects both spermatogonial stem and testicular tumor cells and uncover ways how JMJD5 does so. A likely mechanism is the ability of JMJD5 to facilitate the correct splicing of RNA, which is crucial for proper gene function. Overall, the knowledge gained in this grant proposal may help to overcome male infertility and combat testicular tumors. In particular, JMJD5 inhibitors could be developed for cancer therapy and possibly also as a male contraceptive. Lastly, our studies additionally entail the further development of a method to generate functional sperm in vitro. This could help pre-pubertal males afflicted with cancer, whose treatment leads in about half of all cases to infertility, to retain the ability to procreate. Likewise, this technology holds great promise to allow male genetic disease carriers to produce disease-free offspring.
01/01/2022	Liu	An iPSC-derived human lung tissue model for post-acute sequelae of SARS-CoV-2 infection	The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus has caused over 222 million infections and more than 4.58 million deaths worldwide1 . Although the pandemic is not over yet, the potential profound public health impact of longterm COVID-19 or postacute sequelae of SARS-CoV-2 infection (PASC) is being recognized. The major risk factors for COVID-19 include smoking, aging and comorbidities such as diabetes and hypertension. One of the important tools to study long COVID-19 and test the therapeutics is human lung tissue models as the in vitro cell culture systems and animal models currently used do not completely replicate the pathology of human diseases. However, such models are not currently available. This project will develop a human lung tissue model that are suitable to study long COVID-19 using induced pluripotent stem cells and will contribute to our continuing fights to COVID-19.
01/01/2022	Morales	Examining the role of RNA:DNA hybrids in stem cell DNA repair and maintenance	Stem cells are a unique type of cell population that forms the basis of the human body. Stem cells have an increased life span. Stems cells have also evolved in a way to counter act the increased attacks to DNA that occurs due to increased life span, because loss of stem cells can impair repair of injured organ tissue. These attacks to stem cell DNA come from a variety of different sources, such as replication and normal cellular metabolism. Yet, an understudied source of DNA insults comes from transcription. Using cancer cells, we found that the 5'-3' exoribonuclease XRN2 is an important for efficient DSB repair. XRN2 also controls RNA:DNA hybrid (R-loops) formation, a transcription associated DNA lesions that can result in DSB formation and genomic instability during DNA replication. Lastly, we have found that XRN2 is involved in cell movement. This grant proposal intends to study how XRN2 and RNA:DNA hybrids are in involved in DSB repair, R-loop formation and pluripotency is stem cells.
01/01/2022	Rudolph	Programming adipose stem cells to protect against diet induced obesity	One in five preschoolers is already obese, and recent predictions indicate half of them will become obese by the age of five. More than 55% of US infants born today are predicted to become obese by 35-years old. The hallmark of obesity is too much adipose (fat) tissue. The way adipose tissues respond and grow during excessive food intake is established early in life. Our proposal investigates how specific dietary fats (omega-6 or omega-3) present in early-life nutrition program the way adipocytes (fat cells) develop and grow throughout life. Adipocyte Stem Cells (ASCs) are vital to this process. Early-life dietary fats 'program' the way babies accumulate adipose tissue. Through state-ofthe-art technology and approaches, we discover how ASCs are programmed and why respond differently when triggered to build new adipose tissue. Previously, we determined that ASCs programmed by omega-3 fats were more likely to burn dietary fats for energy rather than store fat. Moreover, ASCs programmed by omega-3 fats had more 'powerplants' (mitochondria) to burn dietary nutrients than omega-6 ASCs did. Our studies are well underway to discovering if the ASC 'nutrient

			burning' fate, programmed by early-life omega-3's, persists when these ASCs are transplanted into an obesogenic host mouse. Using cutting-edge instruments, we will identify molecules and pathways that establish 'nutrient burning,' and we will quantify 'real-time' metabolism in living mice receiving ASC transplants to discover if omega-3 programmed ASCs can improve obesity maladies. Our research paves the way for potential new stem cell therapies that aim to improve whole-body metabolism.
01/01/2022	Sansam	Mechanisms protecting the stem cell genome during cell division	One defining trait of cancer cells is that they continue to divide and grow when normal cells would have stopped. These cells evade or eliminate the internal controls protecting DNA within normal cells from damage during the cell division process. One of these controls is the "replication licensing checkpoint" that confirms whether the cellular DNA is ready to begin the duplication process. The licensing checkpoint is generally inactive in cancer cells, making it an attractive weakness to target for treatment. However, we know almost nothing about how the replication licensing checkpoint works and cannot predict what side effects a targeted cancer chemotherapy would have on adult stem cells. Specifically, we do not know whether adult stem cells have an effective replication licensing checkpoint and whether it protects the genome similarly to differentiated cells. This proposal aims to undercover how the DNA replication licensing checkpoint works and whether adult stem cells use the checkpoint as protection from DNA damage. Achievement of these goals will ultimately help identify better cancer treatments that spare stem cells.
01/01/2022	Yoon	Study of OGDHL-associated neurologic disease using induced pluripotent stem cells	Our bodies are like engines with respect to using energy to function properly. The food we eat provides the fuel for producing this energy. Mitochondria are one of the compartments inside most of our cells that convert food into energy to power our bodies. Defective mitochondria (like defective engines) burn fuel inefficiently and produce by-products that can be toxic to our cells and bodies. Poorly functioning mitochondria are believed to be root causes of many neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease. Children born with defective mitochondria caused by genetic mutations likewise suffer from profound neurological defects including mental retardation, loss of full control of body movements, and stunted growth. Our research focuses on understanding how genetic mutations of mitochondrial components impact energy production and damage brain cells called neurons. We utilize state-of-the-art genetic engineering to introduce these mutations into human adult stem cells. Unlike embryonic stem cells, the use of adult stem cells enables us to research on any tissues including neurons without damaging human embryos. This approach provides us with a powerful experimental system to determine the mechanisms by which specific human mutations disrupt mitochondrial functions and identify and test therapeutics that restore these functions and improve human health.
7/1/2021	Detamore	Condroinductive Peptide for Cartilage Regeneration	Arthritis is the leading cause of disability in the United States. The primary form of arthritis is osteoarthritis, which is often the result of a cartilage injury earlier in life. Solutions to repair cartilage after injury are woefully inadequate, the biggest problem being that an inferior fibrous scar tissue forms instead of true healthy cartilage. We have developed a strategy to modify the surface of a biomaterial that can be placed in the cartilage injury so that the patient's own cells will recognize that biomaterial surface as being favorable for making healthy new cartilage tissue. The beauty of this approach is that no drug delivery is required, which lowers cost for the patient and facilitates translation to the market. This project will examine and enhance specific surface modifications to be tested with rat bone marrow stem cells in the laboratory, enabling future pre-clinical studies to be conducted in the future.
7/1/2021.	Ding	Programming Human IPSC Differentiation into a	Human retina comprises light-responsive neuronal cells called photoreceptors. There are two types of photoreceptors, rods and cones. Rods are responsible for dim light vision, whereas cones are responsible for bright light, color vision, and the ability to distinguish the shapes and details of the things we see. In retinal degenerative diseases, such as retinitis pigmentosa (progressive degeneration of rods), age-related macular degeneration (progressive degeneration of cones, highly

		Photoreceptor-rich cell population for retinal degeneration therapy	relevant to smoking), and diabetic retinopathy (diabetes-induced retinal malfunction, highly relevant to obesity), rods and cones undergo progressive death over time. Although there are many different disease-causing gene alterations and pathological conditions, the progressive death of cones and rods ultimately leads to loss of vision/blindness. There are currently no treatments available for retinal degeneration. Recent stem cell-based photoreceptor transplantation efforts show promise. However, the low percentage yield of photoreceptors derived from the stem cells is a challenge. This project is to determine the potential of developing the adult stem cells, known as human induced pluripotent stem cells (hiPSCs), into a photoreceptor-rich cell population. We will use a protein called COCO to promote hiPSC development. COCO is a multifunctional protein and has been shown to stimulate the development of embryonic stem cells into rods and cones. In this project, we will use COCO combined with modulating the specific regulations of photoreceptor differentiation to promote hiPSC development into a cone- or rod-rich cell population. Completion of the proposed study will demonstrate the potential of hiPSC development into a photoreceptor-rich cell population and help establish the stem cell-based cell therapy for blinding diseases of the retina.
7/1/2021	Gorbsky	Abrupt Aneuploidy Surge in Induced Pluripotent Stem Cells	The application of induced pluripotent stem cells (iPSCs) promises to provide a revolution in medicine. To generate iPSCs, adult cells from a patient are placed into culture and reprogrammed so that they can then differentiate into other cell types. For example skin cells can be reprogrammed so that they can become heart cells. The goal would be to use such cells could be used to replace cells damaged by heart attack. In conventional transplant medicine, patients must be given drugs to suppress their immune systems which might reject the transplant. Because iPSCs are derived from the patient's own cells, immune rejection is avoided. However, there are challenges to wide use of iPSCs. These therapies require that iPSCs be grown extensively under artificial culture outside the body. During cell division in culture, there is the danger that the iPSCs can fail to accurately divide the genetic material, which is carried in the chromosomes. This can cause some products of cell division to have an abnormal genetic content. These genetic defects may render the iPSCs non-functional for therapy, or, worse, cause them to become malignant, generating cancers. One observed abnormality of iPSCs grown in culture is the gain of an additional chromosome. The cells carrying the additional chromosome come to comprise most of the population as they continue to grow in culture. In the past it was thought that this dominance of the population resulted from faster growth of the cells with the extra chromosome such that they would outgrow the normal cells. However, our data, coupled with mathematical modeling, indicate that this explanation cannot account for the rapidity by which cells containing the extra chromosome become dominant. *Instead we hypothesize that during culture of iPSCs, something unknown triggers a large percentage of normal cells to simultaneously gain of the extra chromosome*. *If confirmed, this hypothesis would constitute a major advance in understanding of how genetic changes occur during the culture of iPSCs*. We have iPSCs cells stored before, during, and after the gain of the extra chromosome. Thus, we have an unparalleled opportunity to determine the mechanisms underlying this critical genetic change. Determining the mechanisms by which this abnormality arises among iPSCs grown in culture will foster the development of strategies to suppress it and thus render use of iPSCs in medicine much safer and more effective.
7/1/2021	James	Role of dysregulated myeiopisia in SLE Pathogenesis	Lupus flares are periods when the disease symptoms are worse and lead to increased damage and medication toxicity. Unfortunately, little is known about what causes flares. Neutrophils are a type of white blood cell in blood that may play a role in lupus flares. Lupus patients have increased numbers of stem cells. These stem cells give rise to blood cells that include neutrophils. We have seen that lupus patients with worse disease have higher numbers of immature neutrophils in blood that can go on to become mature cells. Lupus patients also have higher levels of proteins called cytokines that help generate neutrophils. In this project we will

			test if stem cells from lupus patients and lupus cytokines make more neutrophils. We will test if these neutrophils from patients can activate cells that make antibodies and cause damage in lupus. With these studies we can understand how the cytokines detected in lupus patients can eventually cause flares in lupus patients. These studies can help find new treatment options for preventing organ damage in lupus patients.
7/1/2021	Srinivasan	Mechanisms of heart valve dysfunction	Human hearts have four valves. Defects in heart valves could lead to severe health problems before or after birth. Heart valves also degenerate with age. Valve defects are observed in ~8% in individuals >65 years old and ~13% in those who are >75. Thickening of heart valves is one of the most common diseases of the elderly. The causes for this disease are unknown. We have discovered that a gene called as Prox1 is expressed in the heart valves, and the deletion of this gene results in valve thickening in aging mice. To the best of our knowledge this is the first model that closely resembles the human valve disease. In this work we will define the mechanisms by which Prox1 prevents valve thickening. We will also determine if an available FDA approved drug could be used to prevent valve thickening in mice lacking PROX1. Hence, this proposal is consistent with the goals of OCASCR as it seeks to develop a regenerative medical technology to treat a human disease.
7/1/2021	Walters	HEYL Function in Airway Epithelial Differentiation, Regeneration and Disease	Chronic obstructive pulmonary disease (COPD) is a major cause of death in Oklahoma and the US. The disease is typically caused by cigarette smoking, which damages the airways and lung. Currently, there is no cure for COPD or therapy to repair damage to the airways and lung. Specialized epithelial cells line the airway providing a protective barrier to the outside world. This barrier includes secretory and ciliated cells which protect the lung from pathogens (i.e., bacteria and viruses) and harmful environmental factors, such as cigarette smoke and air pollution. A balance in the number of each cell type is critical to maintaining a healthy airway and lung. Cigarette smoking damages and alters the structure of the airway epithelial cell layer. In response to damage, resident adult stem/progenitor cells repair the airway epithelial cell layer by changing into the types of cells that need replacing, via a process termed “differentiation”. However, the stem/progenitor cells from people with COPD are defective and the inability of these cells to repair the airway epithelium correctly has a significant negative impact on the health of people with COPD. Our study will give us a better understanding of how adult airway stem/progenitor cells from COPD patients are defective. In turn, this knowledge will help the development of new stem cell-based regenerative medicine therapies to repair damage to the airway epithelium and treat people with COPD.
7/1/2021	Zimmerman	Research to study how fetal and adult stem cells in mice become tissue macrophages	Macrophages are immune cells that help protect the body from infection and control disease progression. One interesting observation about macrophages is that where they come from (i.e. their origin) influences how they contribute to disease progression. This means that macrophages from one origin may do things that make the disease worse while macrophages from a different origin may do things that may make the disease better. Because of this, it is critical that we understand where macrophages come from in both health and disease. Based on previous work, it is believed that macrophages come from either stem cell or non-stem cell origins. In this proposal, we will test this hypothesis in healthy mice using a newly generated model that specifically labels macrophages from stem cell origins. We are also trying to understand if the macrophage origin impacts their location and gene expression. Future goals of this research are to understand how macrophages from each origin change during disease and to identify ways to block macrophages from one origin (i.e. the bad macrophages) while allowing macrophages from the other origin (i.e. the good macrophages) to persist. Thus, our studies may have a significant impact in multiple tissues and diseases.
01/01/2021	Gorman	Mechanism of IFIH1 promoting systemic lupus erythematosus pathogenesis	Systemic lupus erythematosus (SLE or lupus) is a complex autoimmune disease resulting from a combination of inherited genes and environmental exposures. Viral infections and high levels of inflammatory mediators have been associated with SLE. Immune cells sense viruses and respond by producing inflammatory mediators. DNA variations within viral sensing pathways are linked to an

			increased risk for SLE, including one located in the viral sensor, IFIH1. How this IFIH1 variation may promote SLE remains unclear. Previously, we have shown increased inflammatory markers in healthy individuals with this DNA variation. Further, we showed that a novel mouse model expressing the IFIH1 DNA variation exhibited elevated inflammation. These mice also exhibited prolonged disease markers, called autoantibodies, in a lupus model. This novel IFIH1 mouse model provides us with a unique chance to determine how the DNA variation changes the immune system to promote lupus. In this study, we will examine how inflammation impacts the cells producing the autoantibodies, B cells, in the variant mice and how IFIH1 DNA variation alters the function of human immune cells to promote SLE. We will use primary human immune cells, a novel mouse model, and human stem cell lines to gain information that may lead to therapies for SLE and other autoimmune diseases.
01/01/2021	Hunter	Defining the role of the intestinal barrier in necrotizing enterocolitis using human enteroids	Necrotizing enterocolitis (NEC) is a deadly disease of the newborn, and affects 5-7% of babies in neonatal intensive care units. Prematurity and an abnormal response to bacteria in the gastrointestinal tract contributes to NEC. A strong intestinal barrier is the first line of defense against infection from the external world. In this application we propose generating enteroids (mini intestinal units) from human stem cells collected from infants and older patients. We describe a series of novel experiments to test these enteroids for susceptibility to NEC, by treating them with factors recognized to trigger NEC. We will determine the effect of these triggers on the gut barrier and measure inflammation. We anticipate that the stem cell-derived human intestinal enteroid model of NEC will demonstrate a decrease in normal barrier function, and that strengthening this barrier will be protective against NEC. The use of intestinal enteroids from human subjects will provide tremendous translational power and allow us to gain insight into the molecular, cellular, and organ-level determinants of NEC. The goal of this project is to gain insight into why some babies get NEC and to identify targets for therapeutic intervention using an enteroid model generated from human stem cells.
01/01/2021	Koehler	Intestinal Microbiome and Regeneration in Opioid Misuse	The human intestine is home to trillions of bacteria. These bacteria are the main part of the human gut microbiome. Recent research has shown that the gut microbiome is important for human health and disease. For example, unhealthy changes in the gut microbiome might play a role in cancer, obesity, and heart disease. Intestinal stem cells are keeping the intestine intact, so it can safely house the gut microbiome. We will examine how the microbiome influences the function of intestinal stem cells. Most importantly, we also will study the effects of opioids on the gut microbiome and stem cells. Use and misuse of opioids can cause severe intestinal side-effects. However, little is known about how these drugs affect the stem cells and gut bacteria. We hypothesize that opioids alter the microbiome and may change the number and function of active stem cells. We will use DNA sequencing to identify the bacteria in the microbiome and immunological methods to characterize the intestinal stem cell activity. This project could lead to the discovery of new ways to treat or prevent opioid side-effects and may even provide new information for opioid addiction research.
01/01/2021	Liu	Development of a COVID-19 human lung tissue model for drug screen using iPSCs	The ongoing coronavirus disease 2019 (COVID-19) pandemic is caused by the newly identified coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). People who smoke or have cigarette smoke-related lung diseases are more vulnerable to COVID-19 and are at greater risk of severe illness from COVID-19. There is an immediate need to develop novel therapeutics to combat this rapidly progressive disease. Drug repurposing represents a quick and promising approach for identifying therapeutics for new diseases from among existing drugs, particularly during pandemics such as the current COVID-19. Very few of the drug candidates that are discovered in the laboratory advance to the bedside because cell culture systems and animal models used in laboratory research do not completely replicate the pathology of human diseases. Appropriate

			human tissue models are critical in discovering new drugs. This project will develop a human lung tissue model using induced pluripotent stem cells for COVID-19 research and use it to screen FDA-approved drugs for treating COVID-19. The human lung tissue model can also be applied to other lung disease research such as lung cancers.
01/01/2021	Rajala	PKM2 promotes stemness of Müller Glial Cells in the Retina	The retina is a thin film in the eye that lets us see objects. It is composed of several neurons (nerve cells that send and receive electrical signals) that cannot regrow if they are lost. In several retinal diseases, these neurons die, causing blindness. Risk factors such as smoking, environmental, and genetic stress prompt production of non-functional proteins that result in retinal diseases. Photoreceptors are a type of retinal cell that absorbs light and processes images through co-ordination with other retinal cells. Müller cells are supporting cells that can convert into any other retinal cells if we provide suitable conditions. Our laboratory has found that pyruvate kinase, an enzyme, promotes the conversion of Müller cells into other retinal cells. The purpose of this grant is to study how pyruvate kinase works with Müller cells in replacing the dead neurons in retinal diseases. Vision loss affects millions of people each year. Current treatments only delay vision loss; they do not prevent it. Our goal is to preserve vision through promoting Müller cell conversion to other retinal cells to replace dying retinal cells in retinal diseases.
01/01/2021	Rudolph	Programming Adipose Stem Cells to Protect Against Diet Induced Obesity	One in five preschoolers is already too fat. Recent predictions indicate half of these children will become obese by age five, and more than 55% of infants born today may become obese by 35-years old. The hallmark of obesity is too much fat tissue. The way fat tissues respond and grow during excessive food intake is established very early in life. Our proposal studies how various dietary oils present in early-life nutrition change the way fat cells develop into fat tissue throughout the lifespan. “Fat Stem Cells” are directly changed by oils in the early-life diet that can adversely affect the way fat tissue works. Using several state-of-the-art ways to study these “Fat Stem Cells,” we will understand how these cells become altered by dietary oil composition when they are triggered to build new fat tissue. Accordingly, we will test if certain dietary oils promote accumulation of excessive fat tissue or if they establish ways to burn nutrients for energy. We use specialized mice to manipulate the composition of dietary oils consumed early in life, and we then measure the sizes of fat cells and the ways they use their fuels for storage or energy. We will discover if changes in “Fat Stem Cells” are long-lasting by transplanting these cells into adult mice. This research will pave the way for new stem cell treatments of individuals afflicted with obesity. Ultimately, improving whole-body metabolism using “Fat Stem Cells” will be a major advance and may unlock new therapeutic strategies preventing obesity.
01/01/2021	Subramanian	The role of hypothalamic senescence in obesity induced loss of neural stem cells	Obesity can lead to high blood pressure and heart diseases. It is well known that the central nervous system plays an important role in controlling blood pressure. Over-activity of the nervous system is commonly observed in obese patients and could lead to an increase in blood pressure. Currently, no interventions exist to prevent or reverse obesity-related nervous system over-activity. There is a small population of cells within the brain called neural stem cells. These cells are responsible for creating new neurons as we get older. Studies suggest that there is a reduced number of these neural stem cells in obese patients. However, it’s not clear what contributes to this decrease. Our recent studies in mice suggest that a special type of cells called “senescent cells” that promote inflammation could be responsible. Based on initial evidence, we believe obesity increases the senescent cells in the brain leading to inflammation and thereby reducing the number of neural stem cells. This decrease in the neural stem cells could affect the function of the nervous system that controls blood pressure. In aim

			1, we will examine the effect of dietary obesity on neural stem cell survival and proliferation in relation to nervous system function. In aim 2, we will determine the role of cellular senescence in the brain in mediating neural stem cell loss. Our proposal will likely identify important mechanisms and highlight novel strategies for using neural stem cells as therapy for treating obesity.
01/01/2021	Unnikrishnan	Short-term dietary restriction rescues the age-related decline in intestinal stem cell regenerative capacity	Stem cells are critical in maintaining tissue health. The loss of stem cell function occurs with age. Therefore, preserving stem cell function could be an important approach to delay aging. Dietary restriction (DR) has been shown to slow aging and increase lifespan. DR has also been shown to improve stem cell function, e.g., intestinal stem cells (ISCs). The premise of this application is that short-term DR improves ISC function and that it prevents the age-related decline in ISC function. We propose that short-term DR improves ISC function by altering the types of ISCs, such that there are ISCs poised to become intestinal tissue. We will first characterize the duration of DR required to rescue the age-related decline in ISC function in old mice. Second, we will characterize the different types of ISCs and determine if short-term DR induces changes in the types of ISCs in old mice. The goal of this project is to collect preliminary data that will be used to obtain funding from National Institutes of Health.
01/01/2021	Wang	White to brown adipocyte conversion via chemical-targeted PPAR deacetylation	Obesity and obesity-caused insulin resistance are the key driving forces for type 2 diabetes and other metabolic disorders. Preventing obesity and improving insulin resistance are the most effective therapeutic ways for treating these disorders. White fat cells store energy, while brown fat cells consume energy. Changing white fat cells into brown cells has emerged as a good strategy to fight obesity and insulin resistance. However, to date there are no drugs approved for making more brown cells. Moreover, the cellular origin of brown fat cells and the mechanisms of their conversion remain unclear. In this application, we will use chemicals to make brown cells from white fat cells. We will study how this new method makes more brown cells in this grant. Completion of this proposal will establish a foundation to combat obesity and help create a healthier Oklahoma.
07/01/2020	Bhattacharya	Exploring the unknown biology of KRCC1; a role in DNA damage response and repair	In majority of treated ovarian cancer patients, the disease relapses after a short period with more aggressive stem-like features making it resistant to any drug. Over the years, research has focused on a limited number of known targets and drug development is lagging. Hence there is an urgent need to identify and characterize new targets for use in clinics. We have recently discovered that KRCC1, a protein of unknown biology is a potential cancer target. Ovarian cancer patients with low levels of KRCC1 in the tumor live longer, with lesser chances of relapse and those with higher levels show resistance to chemotherapy drugs. We also found that KRCC1 promotes the DNA damage response and DNA repair, two mechanisms that are required for cancer cells to survive. Therefore, we hypothesize that depleting KRCC1 may kill cancer cells effectively and prevent resistance when combined with chemotherapy drugs. Here we want to study how KRCC1 regulates the damage response and DNA repair using ovarian cancer as a model system. To facilitate clinical translation, we will find candidate drugs that when combined with KRCC1 depletion will effectively kill ovarian cancer cells. With this strategy, in the long-term we hope to combat resistance to chemotherapy and thereby prevent relapse.
07/01/2020	Cai	Ocular Immune Responses to Transplant of iPSCDerived RPE	Stem cell-based therapy is potentially a new treatment for age-related macular degeneration (AMD), a major blinding disease in elderly people. Smoking substantially increases the risk of AMD development and progression. AMD is resulted from the loss of retinal pigment epithelium (RPE). Other than RPE replacement, currently there is no effective treatment that can slow down the degeneration process in AMD. In the past decade methods of generating RPE from reprogramed adult cells have been established and optimized. For practical reasons RPE cells used for transplant usually are not originated from the same patient. The back of the eye has unique immune regulatory mechanisms and it is expected that the transplanted cells can survive without long-term use of

			immunosuppressive drugs. As we learned from the ongoing clinical trials, however, the immune tolerance is not always achieved and the underlying mechanisms are unknown. In this application we have proposed an innovative hypothesis that in eyes with AMD-like injury, regulatory T cells can be activated and support the survival and function of the transplanted RPE cells. Experiments are designed to test the immune responses to transplant of RPE derived from induced pluripotent stem cells in mouse models of AMD, and to examine the functional roles of a specialized type of T lymphocytes that can be activated by retinal injury and exert protective effects to the outer retina. Findings from our studies will open a new research area with a focus on modulating T cell function as an important ancillary therapy in regenerative medicine.
07/01/2020	Ding	Programing human iPSC differentiation into a cone-rich cell population for retinal degeneration therapy	Human r0tina comprises light-responsive neuronal cells called photoreceptors. There are two types of photoreceptors, rods and cones. Rods are responsible for dim light vision, whereas cones are responsible for bright light, color vision, and visual acuity. In retinal degenerative diseases, such as retinitis pigmentosa, age-related macular degeneration (highly relevant to smoking), and diabetic retinopathy (highly relevant to obesity), rods and cones undergo progressive death over time. Although there are many different disease-causing gene alterations and pathological conditions, the progressive death of cones ultimately leads to loss of vision/blindness. There are currently no treatments available for retinal degeneration. Recent stem cell-based photoreceptor transplantation efforts show promise. However, the low percentage yield of cones derived from the stem cells is a challenge. This project is to determine the potential of differentiating the adult stem cells, known as human induced pluripotent stem cells (hiPSCs), into a cone-rich cell population. We will first use a protein called COCO to promote hiPSC differentiation into a cone-rich cell population. COCO is a multifunctional protein and has been shown to stimulate stem cell differentiation into photoreceptor precursors/cones. The retina-specific gene expression regulators NRL and NR2E3 are the main inhibitors of cone differentiation. We will suppress NRL and NR2E3 activity in hiPSCs to promote differentiation of these cells into a cone-rich cell population. Completion of the proposed study will demonstrate the potential of hiPSC differentiation into a cone-rich cell population and advance the development of the stem cell-based cell therapy for blinding diseases of the retina.
07/01/2020	Humphrey	Role of TRPC1 in Regulating Mesenchymal Stem Cells and Bone Regeneration	Bone breaks are common and increase with the age. 10-15% of bone breaks never heal and become non-union resulting in multiple surgeries and patients being unable to walk or use their broken arm. Obesity, smoking, and alcoholism all increase the risk of non-union bone healing. Unfortunately, these risk factors are very common in our Oklahoma population. There is a big need for new ways to solve non-union fractures and this can only be done through a better understanding of bone repair and regeneration. When bone tissue is injured, adult bone mesenchymal stem cells (MSC) move to the site of injury by signals coming from the broken bone including high calcium levels and a small protein called platelet-derived growth factor (PDGF). It is not known how these signals are controlled in the MSC to drive the best bone healing. We believe that part of MSC regulation is by a protein channel called transient receptor potential canonical channel 1 (TRPC1) that boosts cell reaction to high calcium and PDGF making more MSC that can repair bone. We study mice lacking this protein in their MSCs to understand how they are involved in making new bone. By understanding the work of MSCs, we hope to improve therapies for non-union bone breaks.
07/01/2020	Srinivasan	Defining the mechanisms of functional interaction between a gene and diet in the onset of obesity	In the United States, it is estimated that one-third of adults and one-sixth of children are obese. Obesity is a risk factor for cancer and cardiovascular diseases such as diabetes and stroke with an economic impact of more than $100 billion per year in the United States alone. Hence, better understanding of the mechanisms that regulate obesity and approaches to treat this disease are urgently needed. Increased availability and consumption of calorie rich diets has contributed to the increased prevalence of obesity. However, there is wide variation in the prevalence of obesity among individuals eating the same type of diet. This observation suggests that both diet and genes regulate obesity. We have identified a gene that regulates how body responds to diet. We will test whether this gene is necessary for the skeletal muscles to burn calories and prevent the onset of obesity.

01/01/2020	James	Role of dysregulated myelopoiesis in SLE pathogenesis	Lupus flares are periods when the disease symptoms are worse and lead to increased damage and medication toxicity. Unfortunately, little is known about what causes flares. Neutrophils are a type of myeloid cells in blood that may play a role in lupus flares. Lupus patients have increased numbers of stem cells that express a protein CD34 on their surface. CD34 cells give rise blood cells that include myeloid cells. We show that lupus patients with worse disease have higher numbers of immature neutrophils in blood. These patients also have higher levels of proteins called cytokines that induce CD34 cells to generate myeloid cells. Immature neutrophils are an intermediate cell type when CD34 cells develop into neutrophils. Therefore, we will test if the CD34 cells in lupus patients give rise to higher numbers of immature neutrophils. We will also test if the cytokines that are higher in lupus patients with worse symptoms can increase the myeloid cells generated by CD34 stem cells. We will test if the neutrophils produced with lupus cytokines can activate B cells, which make antibodies that cause damage in lupus. We will use induced pluripotent stem cells (iPSC) that we have generated by genetic modification of adult blood cells in culture. These studies will provide valuable information about the ability of stem cells and lupus cytokines to induce B cell activating cells that may worsen the lupus symptoms and cause flares. The understanding of how these neutrophils are generated can lead to novel therapeutic targets.
01/01/2020	Lee , CF	Roles of Cellular Senescence and NAD in Regenerative and Repair Mechanisms of Disease Hearts	Unhealthy diet (diet with high-fat, sugar, salt) and/or smoking cause obesity, diabetes and high blood pressure, all of which are risk factors for cardiovascular disease. People with these risk factors have worse outcomes and higher chances of heart failure after heart attack. Adult heart muscle cells have little regenerative power. However, expansion and differentiation of other cell types (e.g. fibroblasts and immune cells) in the heart are triggered during the repair and recovery phase after heart attack. An explosion of evidence shows that interventions that elevate the level of NAD+, an essential metabolite for cellular energy production, is therapeutic to many diseases. Importantly, elevation of NAD+ levels improves mitochondrial and skeletal muscle stem cell function, which in turn reduces cellular senescence, an aging process of cells. Removal of senescent cells by the immune system plays a positive role in tissue regeneration. In this proposal, we will test whether and how high-fat diet and hypertensive stresses prime the heart against regeneration and repair by activating cellular senescence. We will focus on the interplays between cardiomyocytes, fibroblasts and immune cells, and test if boosting NAD+ levels will promote pro-regenerative, anti-senescence mechanisms. Our group has the expertise and necessary tools to study NAD+-dependent pathways and heart function. This proposal will allow us to explore a new venue in regenerative medicine and generate data to compete for Federal funding. We will further investigate the therapeutic roles of cellular senescence and NAD+ metabolism in repair and regeneration after heart attack in our next R01 proposal.
01/01/2020	Lee, D.	Stem Cell Derived Retinal Ganglion Cell Engraftment into a Post-Uveitic Eye	The delicate light-gathering cells of the eye are exquisitely sensitive to inflammation. Therefore, uncontrolled inflammation of the eye can damage or destroy these light gathering cells, such as the optic nerve. Unfortunately, in some patients even once the inflammation has subsided, irreversible damage to the optic nerve has occurred, resulting in permanent blindness. In an effort to restore vision in these patients, stem cell derived nerve cells have been successfully derived. In addition to the damage to the nerve cells the inflammation causes additional changes to the eye that make it difficult to accept the healthy stem cell derived nerve cells. As such, the next hurdle to restoring vision in these patients is the administration of these cells without rejection into an eye that has been damaged by inflammation. We propose to administer these stem cell derived nerve cells into an eye that has been inflamed and determine the optimal conditions for their survival and function. We are experienced with ocular inflammatory models and have an established collaboration with a leading stem cell laboratory, so are ideally suited to carry out this project. The successful completion of this proposal will provide additional information about tissue specific stem cells and how to integrate them into an injured organ with the long-term goal of restoring vision in patients with damaged light-gathering cells.

01/01/2020	Liu	Modeling Influenza Virus Infection Using iPSC-derived Alveolar Organioids	The current in vitro cell culture systems and animal models do not completely replicate the pathology of human diseases, and no appropriate human lung tissue models are readily available. As a result, very few of the drug candidates that are discovered in the laboratory advance to the bedside. This project will develop a human lung tissue model using induced pluripotent stem cells for respiratory diseases research and thus accelerate the development of medicines to treat these diseases.
01/01/2020	Olson AL	PFKFB# regulation of glycolysis and glucose uptake in developing adipose tissue in adipocyte stem cell differentiation	The growth of fat tissue during obesity and the growth of tumors during cancer are similar. For example, both fat cells and tumor cells are produced from self-renewing progenitors, or stem cells. Both fat cells and cancer cells utilize high levels of glucose to develop. We hypothesize that glucose is required for synthesizing components that make up new fat cells. We will test this hypothesis using model fat cell precursors and fat cell precursors from mice. These studies will help us learn why some cancers are more common in obesity.
01/01/2020	Pezza	Mechanism and regulation of gene expression mediated by CHD4 in Spermatogonia Stem Cells	Spermatogenesis is the process in which spermatozoa are produced from spermatogonial stem cells and is required for normal testis development and sustained male fertility in adults. Each spermatogonia stem cell will continually divide to create more spermatogonial stem cells that will differentiate to eventually form spermatozoa. Thus, maintaining a healthy population of spermatogonia stem cells is key in both the adult and the developing testis. During spermatogonia stem cell divisions and differentiation, the chromatin (a combination of DNA and proteins named histones) undergo conformation changes, which is necessary for basic processes to occur, such as the production of RNA and ultimately production of proteins. These chromatin changes are controlled by a group of proteins named chromatin remodelers. In this project, we focus our studies in the NURD chromatin remodeling complex, which we propose have a central role in regulating at the molecular level the ability of spermatogonia stem cells to survive and differentiate into more mature types of cells. Specifically, we will test our hypothesis in which Chd4 (the catalytic component of the NURD complex) regulate the amount of RNA produced from a specific group of genes, which function in basic cellular processes such as those directing cell division and differentiation. Additionally, we will investigate how Mbd3, a protein that physically associates with Chd4 to form the NURD complex, affect the activity of Chd4. Our goal is to understand spermatogonial stem cell function, which has great potential for curative genetic treatments, and how they provide sustained male fertility.
01/01/2020	Rankin	Coordination of chromosome structure and DNA replication	Stem cells are defined by two essential properties: first, they are able to make perfect copies of themselves, and secondly they can develop into many different cell types, such as nerve or blood cells, in a process called “differentiation”. For this reason, stem cells offer unprecedented hope for replacing different kinds of damaged or diseased tissues. We are interested in how chromosomes, the long pieces of DNA where genes reside, can be perfectly duplicated during stem cell propagation. How are perfect copies of each chromosome made? How can it happen when the chromosomes are packed tightly into the cell? We have recently discovered a direct physical connection between a glue-like protein that packages chromosomes into the cell, and another protein that is essential for replicating chromosomes. This discovery may provide the critical clue about how chromosome structure and duplication are connected. Here we propose experiments to test what happens when the connection between these proteins is disrupted. This will provide important insight into how the precise duplication of cells is connected to proper chromosome structure, and ultimately how this structure changes when stem cells are induced to differentiate into new cell types.
01/01/2020	Sansam	Mechanisms of Genome Structure Critical for Stem Cell Function	For stem cell therapy to be widely used in medicine, we must first understand the traits that define stem cells and how to harness those characteristics for therapeutic benefit. One such trait is the way that our DNA, or chromosomes, fold inside stem cells. The proper folding of chromosomes into loops is critical for stem cell function. We know that the machinery necessary for the looping of chromosomes is also involved in the process that copies our DNA each time the cell divides. The goal of this grant is to study how DNA replication machinery enables chromosomal folding. This application is for the second year of support for this OCASCR-funded project. During the first year of support, we have built many of the tools necessary for completing key experiments. The second year

			of OCASCR support would allow us to use those tools to show how DNA replication machinery enables chromosomal folding.
01/01/2019	Humphrey	The role of MyoD Family Inhibitor (Mdfi) in the maintenance of hematopoietic stem cells and lineage commitment	During life blood is remade from bone marrow cells called hematopoietic stem cells (HSC). These cells rest in a quite state in the bone marrow and only occasionally make new cells (proliferate). In many diseases like blood cancers, these HSC proliferate too much. Understanding how HSC proliferation is controlled and how stem cells become blood cells may improve our diagnosis and treatment of leukemias and could also be useful in regenerative medicine. Our studies will discover how a protein called I-mfa controls HSC proliferation.
01/01/2019	Lee	Stem Cell Derived Retinal Ganglion Cell Engraftment into a Post-Uveitic Eye	The delicate light-gathering cells of the eye are exquisitely sensitive to inflammation. Therefore, uncontrolled inflammation of the eye can damage or destroy these light-gathering cells, such as the optic nerve. Unfortunately, in some patients even once the inflammation has subsided, irreversible damage to the optic nerve has occurred, resulting in permanent blindness. In an effort to restore vision in these patients, stem cell derived nerve cells have been successfully derived. In addition to the damage to the nerve cells the inflammation causes additional changes to the eye that make it difficult to accept the healthy stem cell derived nerve cells. As such, the next hurdle to restoring vision in these patients is the administration of these cells without rejection into an eye that has been damaged by inflammation. We propose to administer these stem cell derived nerve cells into an eye that has been inflamed and determine the optimal conditions for their survival and function. We are experienced with ocular inflammatory models and have an established collaboration with a leading stem cell laboratory, so are ideally suited to carry out this project. The successful completion of this proposal will provide additional information about tissue specific stem cells and how to integrate them into an injured organ with the long-term goal of restoring vision in patients with damaged light-gathering cells.
01/01/2019	Liu	CRISPRa LncRNA Screen for the Differentiation of Mesenchymal Stem Cells into Alveolar Epithelial Type II Cells	Cigarette smoking is a major risk factor for chronic lung diseases including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). COPD is the third leading cause of death in the USA while IPF afflicts approximately 200,000 individuals in the United States, and an estimated 40,000 people succumb to the disease each year. There are no effective treatment options for both diseases. This research project will identify lncRNAs that can convert mesenchymal stem cells into lung cells to repair lung damages in these diseases via genome-wide CRISPR activation screen. The outcome of this project may provide insights toward the development of new therapy for chronic lung diseases.
01/01/2019	Miller Ben	Do muscle cells need satellite stem cells?	Skeletal muscle cells are unique in that they have many nuclei. The large number of nuclei are needed to support this large cell type. Unfortunately, muscle cells cannot make more nuclei so it is thought that other cells must give nuclei to help muscle grow or to replace damaged nuclei. Therefore, research has focused on a stem cell called a satellite cell because it can give nuclei to muscle cells. However, recent research has shown that when satellite cells are taken away, the muscle grows normally and does not shrink any fasterwith age. In our lab we collected data that show that muscle cells may really have the ability to make more nuclei. However, we are not certain of that finding and have therefore developed new methods to confirm what we think to be true. In this proposed study, we will use new methods to be directly measure the ability of muscle cells to make nuclei without satellite stem cells present. If our studies show that muscle can make their own nuclei without satellite stem cells, there would be a massive shift against current ideas related to nuclei in muscle. Further, the findings would create an entirely new target to treat muscle wasting diseases and the loss of muscle with age. Finally, it leaves open the possibility of the intriguing, but highly unusual, strategy to remove satellite stem cells to start muscle nuclear replication for muscle growth.
01/01/2019	Olson AL	Glucose and nicotinamide metabolism in adipocyte stem cell differentiation	The growth of fat tissue during obesity and the growth of tumors during cancer are similar. For example, both fat cells and tumor cells are produced from self-renewing progenitors, or stem cells. Both fat cells and tumor cells change the ways that they metabolize the B vitamin, niacin, as they mature. We hypothesize that changes in the niacin metabolism signal stem cells to become mature

			cells. We will test this hypothesis using fat cell precursors from mice. These studies will help us learn why some cancers are more common in obesity.
01/01/2019	Pezza	The Role of Chd4 and Chd3 Catalytic Subunits of the NURD Chromatin Remodeling Complex in Spermatogonial Stem Cell Biology and Testis Development	Spermatogenesis is the process in which spermatozoa are produced from spermatogonial stem cells (SSCs) and is required for normal testis development and sustained male fertility. Each SSC will continually divide to create more spermatogonial stem cells (self-renewal) that will differentiate to eventually form spermatozoa. In this process, accurate chromosome segregation is essential so that the appropriate chromosome number is maintained and passed on to subsequent generations. Indeed, errors in producing primordial cells and in chromosome segregation can lead to the production of aneuploid gametes and abnormal spermatogenesis which may result in infertility, is the cause of birth defects, and genome instability, the later is known cause of several testicular tumors. The chromatin remodeling activity of the NURD complex regulates fundamental processes of cell biology, and we propose may have a central role in SSC self-renewal and differentiation. Intriguingly, mammalian testes express two alternative catalytic subunits of NURD complexes, Chd3 and Chd4. The role of Chd3 and in gamete cell development, including SSCs has not yet been studied. In this proposal we will determine how and when Chd3 and Chd4 activities are required for these fundamental aspects of testis development in mammals. Additionally, we will reveal at the molecular level the role of each NURD catalytic subunit in the accuracy of chromosome segregation during any stage of spermatogenesis. The broader goal of our studies is to understand spermatogonial stem cell function, which has great potential for curative genetic treatments, and how they provide sustained male fertility.
01/01/2019	Richardson	Does Dietary Restriction Alter DNA Methylation in Intestinal Stem Cells	Stem cells play an important role in the age-related decline in the regenerative capacities of tissues. Dietary restriction (DR) is an experimental manipulation that retards aging and the progression of most diseases. DR also enhances the maintenance and function of stem cells in a variety of tissues. Because stem cell function has been shown to be epigenetically regulated, we proposed that DR induces changes in DNA methylation in intestinal stem cells at specific genomic regions. The changes in DNA methylation then alters the expression of genes that are potentially important in stem cell function. Over the past 7 months, we developed the methods for isolating stem cells from the intestine. The stem cells are functional as they form mini intestines. We are now measuring DNA methylation in stem cells from control mice and DR mice. An additional year of support is requested to develop the technology to measure gene expression in single cells. This state-of-the-art technology will allow us to analyze the heterogeneity of stem cell populations and to determine if different sub-populations of stem cells arise from DR that is not possible with the current technology. Measuring gene expression in single cells also allows us to discover novel cell types and regulatory networks that might change with DR. This is the first study to investigate the effect of DR on gene expression in single cells. We will then determine if changes in DNA methylation induced by DR are associated with changes in gene expression we see in stem cells.
01/01/2019	Sansam	Mechanisms of Genome Structure Critical for Stem Cell Function	To make stem cell therapy useful for more diseases, we must learn to make stem cells easily from a patient's mature cells and to turn stem cells into more cell types. To do those things, we must first understand how to change the traits that define a cell. One such trait is the way that chromosomes fold in the cell nucleus. Chromosomes fold into loops that bring together different parts of the genome to control gene expression. Intriguingly, the formation of loops requires some of the same cellular machinery that duplicates the chromosomes before cell division. We will use this grant is to study how DNA replication factors promote chromosomal folding. We have data showing that one special DNA replication protein physically interacts with other proteins involved in loop formation, so we will test whether chromosomal folding requires that DNA replication protein. Understanding how DNA replication and structural proteins work together to make chromosomal loops will bring us closer to being able to manipulate chromosomal folding in stem cells.
01/01/2019	Srinivasan	Gene- and stem cell therapiesfor lymphaticdisorders	The mammalian lymphatic vasculature is vital for the return of tissue fluids to the circulating blood. It also absorbs digested lipids from the intestine. Abnormal functioning of the lymphatic vasculature causes swelling of body parts, especially the limbs. This is known as lymphedema, a common

			disorder that results from either mutations in genes that regulate lymphatic vascular development or more often from surgical damage to the lymphatic vessels and valves. Millions of humans are estimated to be suffering with lymphedema in the US alone. Currently, no cure is available for patients with lymphedema; therefore, only palliative treatments like massage are prescribed. Chylous ascites is another disorder caused by defects in the lymphatic vasculature and it is characterized by the swelling of the abdomen due to leakage of fluids from the gut. The goal of this application is to use gene therapy and stem cell therapy approaches to correct lymphedema and chylous ascites in a mouse model, which recapitulates a human syndrome. Knowledge gained from our work might provide an opportunity to harness the potential of adult stem cellsto treat lymphedema.
07/01/2018	Dawson	Stem Cell Genome Uniformity in Individual Organisms	Our bodies contain cells that carry out specialized functions. For example, insulin producing cells. We also harbor stem cells, whose job is to divide to produce more specialized cells. All of our cells carry two sets of chromosomes: one inherited from each parent. Our genes are carried on those chromosomes. Changes, or mutations, to the DNA that makes our genes can affect gene function. If mutations occur in the genes of stem cells, then the specialized cells they produce will also have mutated genes and may not function properly. Some mutations affect single nucleotides, the building block of genes. These mutations are detectable by DNA sequencing. Other mutations can involve duplications, deletions, or rearrangements of large blocks of DNA thousands or millions of nucleotides long, within or between chromosomes. These changes, called large chromosome rearrangements (LCRs), can increase or decrease the numbers of copies of genes, or change the way they work, without changing the genes themselves. Recent studies have suggested that LCRs might occur in each of us, in the earliest cell divisions, generating new chromosome structures. LCRs can’t be detected easily by DNA sequencing so this has been difficult to test. However, a new technology has made it possible to detect LCRs. We propose to use this technology to ask two questions: How often do LCRs occur in eggs and sperm, and how often do LCRs occur during organism growth to create genetically distinct populations of stem cells within the same organism?
07/01/2018	Elliott	Role of Cav1 on the Maintenance of Corneal Epithelial Stem Cell—a New Therapy	We don’t notice our corneal epithelium until we get sand grains in our eyes. This outer most layer of the cornea is the first line of defense to protect our precious sight. This layer of tissue behaves similarly to our skin which renews itself in health and repairs itself when injured. The stem cells which provide this regenerating ability reside in the limbus, which is a ring of 2 mm thin tissue at the border of the transparent cornea and the sclera, the white part of the eyeball. Trauma such as thermal or chemical burns to the eye, infections, or genetic diseases can deplete these corneal stem cells, which results in cloudiness of the cornea leading to corneal blindness. Even though corneal stem cell transplantation is available to treat corneal stem cell deficiency, the procedure is limited to availability of stem cell supply and how well a person can tolerate immuno-suppressive drugs. We discovered that a gene named Caveolin1 is highly expressed on the surface of the stem cells. There are hints that when this gene is absent, the stem cell population may have expanded. The goal of this grant is to unequivocally verify if this is the case and to further understand the underlying process. If indeed Cav1 reduction can expand the stem cell population, we can develop drugs to target this gene as a new therapy to treat corneal stem cell deficiency.
07/01/2018	Gorbsky	Chromosome Instability in Induced Pluripotent Stem Cells	The ability to harvest adult cells from a patient and reprogram them to become pluripotent stem cells has broad promise as a cure for many critical human health problems including maladies such as

			heart disease and spinal cord damage. A key feature of this approach is that the induced pluripotent stem cells (iPSCs) must be grown for many generations under artificial culture conditions in a laboratory incubator before being used in the patient. During this time the dividing iPSCs can develop chromosome abnormalities of several types. These chromosome defects may render the iPSCs non-functional for therapy, or, worse, cause them to become malignant, generating cancers. While chromosome defects in iPSCs cells in culture have been widely reported, there is little information about potential environmental causes. Similarly, there is almost no understanding of the important biochemical pathways in cells that generate these chromosome abnormalities in iPSCs. Understanding how iPSCs undergo chromosome changes during culture is essential for their safe use. This project will apply innovative new technologies and analysis platforms for characterizing the different chromosome abnormalities that arise during growth of iPSCs in culture. It will provide information about potential environmental causes and map the biochemical pathways within cells that lead to these defects. This information is essential in designing methods to prevent chromosome abnormalities from arising in iPSCs during culture.
07/01/2018	Griffin, T.	Effect of obesity and aging on adult chondrocyte progenitor cells	Osteoarthritis is a major cause of disability as we age. It affects joints throughout the body, especially the knee. A central feature of osteoarthritis is the loss of articular cartilage, which is the smooth, rubbery tissue that cushions the ends of bones during movement. Obesity speeds up the loss of cartilage and causes pain that makes it even more difficult to exercise and lose weight. There are currently no treatments that slow down cartilage loss, which is especially needed with obesity. The long-term goal of this study is to learn how obesity and aging reduce the ability of cartilage to heal itself. The focus of this proposal is on adult stem cells that give rise to cells that make and repair cartilage (i.e., chondrocyte progenitor cells or CPCs). These cells are present in the surface zone of articular cartilage and the adjacent synovial tissue. They give rise to new chondrocytes during growth, and they migrate to sites of cartilage damage following joint injury. Cartilage has no blood supply so the ability of CPCs to migrate to damage sites is critical for repair. We think that obesity speeds up cartilage loss by reducing the ability of CPCs to migrate to injury sites and mature into chondrocytes that produce cartilage structural proteins. We will test this idea by tracking the number and function of CPCs in obese mice and high-fat CPC culture models that mimic metabolic aging. This research may lead to new treatments that preserve CPC function and delay cartilage loss.
07/01/2018	Olson, L.	ENABLING-New technology for generating transgenic mice by manipulating the male germline	Transgenic mice are some of the most important tools for studying adult stem cells. Mice can be genetically engineered to “knock out” genes from stem cells, to express new genes in stem cells, or to label stem cells with fluorescent probes for tracking stem cell fate over time. However, generating new transgenic mice is time consuming and expensive, and this has always been a limiting factor. The goal of this proposal is to establish a new technology for making transgenic mice at the Oklahoma Medical Research Foundation and the University of Oklahoma Health Sciences Center. The classical approach to make transgenic mice is to inject DNA into an early mouse embryo and then implant then embryo into a female host to complete embryonic development and live birth. Embryo manipulation is technically difficult and requires a large, expensive mouse colony to generate embryos and female hosts. We propose to use a different approach whereby transgenic DNA is introduced via retroviral particles into the male mouse testes. These mice will then be used as breeding studs to transmit the transgenic DNA into offspring. In this Enabling Technology grant, we propose to establish the new technology by generating transgenic mice for a gene called Zfp521,

			which will advance our understanding of how adult stem cells contribute to scar tissue formation and postnatal bone growth. This is related to currently funded projects in the Olson lab including an NIH/R01 grant (for scar tissue) and an OCASCR project (for bone growth).
07/01/2018	Olson	PDGF signaling in Skeletal Stem Cells and Postnatal Bone Growth	Bones seem like fixed structures because they are hard and they persist long after death, but in fact they are surprisingly dynamic and undergo complete turnover 3-5 times between skeletal maturity and death. Also, bone fractures can heal, and in fact they heal more completely than injuries to most other tissues. The turnover and healing ability of bones is possible because they harbor adult skeletal stem cells (SSCs). These cells are sometimes called mesenchymal stem cells. SSCs reside inside bones, and they are multipotent, meaning they can turn into different cell types for instance osteoblasts (bone forming cells), chondrocytes (cartilage forming cells), and adipocytes (fat storing cells). The field of regenerative medicine has been keenly interested in SSCs for decades, but there is still so much we do not understand about how they are regulated and how they might be used for therapy. The Olson laboratory studies a growth signal called platelet-derived growth factor (PDGF), which binds to PDGF receptors (PDGFRs) on the surface of many cell types. It was recently discovered that SSCs have PDGFRs, but the role of this growth signal has not been carefully studied in SSCs and adult skeletal biology. Mutations that increase or decrease the level of PDGFR signaling activity results in increased or decreased bone growth. This suggests that PDGFR signaling causes SSCs to behave abnormally. The goal of this proposal is to develop a better understanding of how the level of PDGF signaling controls SSC self-renewal and fate. These experiments are is important for developing SSC-based therapy.
07/01/2018	Rankin	Esco1 and PARP1 cooperate to regulate chromosome structure	Stem cells are defined by two essential properties: first, they are able to make perfect copies of themselves, and secondly, they can develop into many different cell types, such as blood or nerve cells, in a process called “differentiation”. We are interested in how the structure of chromosomes, the long pieces of DNA where genes reside, changes when cells differentiate. Changes in chromosome structure lead to changes in the collection of genes that are turned on, thereby altering the identity of a cell: nerve cells turn on nerve genes, muscle cells turn on muscle proteins, etc. Because chromosomes are so much longer than the nucleus in which they are stored, they are compacted by the formation of loops, and it is the arrangement of these loops that helps determine what genes are active. The molecular glue that tethers chromosome loops is called Cohesin. We have discovered that the Cohesin regulator Esco1 cooperates with a protein called PARP1 to dramatically alter chromosome structure and thus cell identity. PARP inhibitors are currently in use as anticancer therapy, but the precise manner in which cells respond is not clear. We believe our current studies will provide important new information about how PARP and cohesin regulate chromosome structure and cell fate.
07/01/2018	Xia	Role of O-glycan Sialylation in Protection of Intestinal Stem Cells and Their Niche	Colon cancer remains a leading cause of cancer-related deaths in the US. Cancer arises from normal cells lining the colon wall, called epithelial cells. Normal epithelial cells come from colon stem cells; tumor epithelium is thought to come from tumor stem cells. Both stem cell types need a special “home”, or niche, which is made up of neighboring cells that deliver special signals that direct their growth and survival. However, the cells making up this niche, and how they control stem cells in healthy and cancer tissue is not clear. All cells are covered with sugars, called glycans. One special glycan is called sialic acid. This acts as a “cap” to glycan chains on particular proteins called “glycoproteins”, making them acidic. We found that the healthy colon stem cell niche is surrounded

			by sialic acid-producing cells. Using an innovative genetic approach to generate mice lacking the ability to cap glycoproteins with sialic acid, we found this totally changed the colonic stem cell niche, making it less acidic, and causing more cells to divide. Surprisingly, a subset of mice developed tumors. This suggests sialic acid is crucial for maintaining a healthy colon stem cell niche and preventing it from turning it into a tumor-promoting niche. We will use our unique intestinal sialic acid-deficient mouse to determine how this important sugar protects colon stem cells. We envision our proposed studies will give insight into how we may alter stem cell niches (e.g. through dietary sialic acid) to prevent or treat colon cancer.
07/01/2018	Zhang	How Integrin Regulates the Adipogenesis of Mesenchymal Stem Cells	Fat tissues and fat cells are important for health, and abnormal formation and turnover of fat tissues and fat cells are associated with various diseases and/or susceptibility of diseases such as diabetes and heart diseases. After birth, fat cells are originated from a type of source cells called mesenchymal stem cells. How this type of stem cells becomes fat cells is still unclear. But understanding how this type of stem cells becomes fat cells and form fat tissue is quite important for us to change the formation and turnover of fat tissues in our bodies. Recently, we found that a group of candidate proteins can promote the formation of fat cells from their source cells, i.e., mesenchymal stem cells. In this study, we will find out exactly which one of these candidate proteins promotes the formation of fat cells. Then, we will figure out how this key protein promotes the formation of fat cells. From this study, we will likely discover an important regulator for the formation and turnover of fat tissues. This regulator will have a great potential to be clinically beneficial for disease intervention. The knowledge and conclusion from this study will also be significant for preventing various diseases as described above. Moreover, the outcome of our study will be very useful for cosmetic and fitness purposes.
01/01/2018	Freeman	Epigenome of Neural Stem Cell with Aging	Neural stem cells in the brain are the source of the new neurons, and other cells, required for proper learning and memory. This process of generating new neurons occurs throughout life but becomes impaired with aging. This declining ability to generate new neurons is a potential causative mechanism for cognitive decline with aging and neurodegenerative diseases such as Alzheimer's. In our current adult stem cell research we are exploring the hypothesis that alterations to the genome with aging, epigenomics are responsible for the declining ability of neural stem cells to reproduce and generate new neurons. The studies proposed here will achieve two important goals to make this work competitive for funding from foundations and federal agencies. First we will generate a unique mouse model where neural stem cells can be rapidly isolated from the brain and analyzed. In the second aim we will validate the model system for using a variety of approach including a new technology to examine thousands of cells individually within a sample. The short term goal of this research is to continue our scientific aims and obtain long-term external funding. The long term goal of our work is to target the neural stem cell epigenome to restore a 'youthful' state to maintain brain health with aging.
01/01/2018	Humphrey	The role of MyoD Family Inhibitor (Mdfi) in the maintenance of hematopoietic stem cells and lineage commitment	During life, blood is remade from bone marrow cells called hematopoietic stem cells (HSC). These cells rest in a quite state in the bone marrow and only occasionally make new cells (proliferate). In many diseases like blood cancers, these HSC proliferate too much. Understanding how HSC proliferation is controlled and how stem cells become blood cells may improve our diagnosis and treatment of leukemias and could also be useful in regenerative medicine. Our studies will discover how a protein called I-mfa controls HSC proliferation.
01/01/2018	James	Using Circulating Progenitor Cells to Examine the Role of Stem Cell Factor (SCF) in SLE pathogenesis	Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by immune cell dysfunction. Our recently published research has identified that the protein stem cell factor (SCF) is increased in SLE patients. SCF is a ligand that interacts with its receptor, c-kit (also called CD117). Previous research has shown that this interaction helps replenish stem cells that eventually become immune cells (hematopoiesis) and that some immune cells that participate in the immune response (to fight infection or cause autoimmune disease) express CD117 on their surface. We see that SCF

			interacting with CD117 on immune cells causes a pro- inflammatory response that is increased in SLE patient cells. Despite this knowledge, very little is known about how SCF contributes to SLE pathogenesis. This project will determine underlying signals that result in a pro-inflammatory response in immune cells expressing CD117 from SLE patients compared to healthy individuals. We will also determine the ability of SCF to activate progenitor cells (stem cells in the blood that express CD117 and can become immune cells) to help them differentiate into immune cells in SLE patients compared to healthy individuals. Once differentiated, we will determine if cells from SLE patients are more inflammatory than those from healthy individuals.
01/01/2018	Olson. Al	Role of nicotinamide metabolism in differentiation of adipocyte stem cells	The growth of fat tissue during obesity and the growth of tumors during cancer are similar. For example, both fat cells and tumor cells are produced from self-renewing progenitors, or stem cells. Both fat cells and tumor cells change the ways that they metabolize the B-vitamin, niacin, as they mature. We hypothesize that changes in the niacin metabolism signal stem cells to become mature cells. We will test this hypothesis using fat cell precursors from mice. These studies will help us learn why some cancers are more common in obesity.
01/01/2018	Pezza	Epigenetic Control of DNA Repair in Cancer Stem Cells.	Recent advances in cancer research have suggested that within a tumor a specific subset of cancer cells named Cancer Stem Cells can regenerate a tumor even after anti-cancer therapies. Therefore, targeting CSCs at the initial steps of cancer treatment may greatly reduce the incidence of cancer recurrence. Current anti-cancer treatments use radiation or chemicals to break the DNA (DNA damage). We think that CSCs evade or resist current anti-cancer treatments because they utilize DNA repair systems in an unconventional way. We propose to study how CSCs utilize alternative DNA repair machineries present in the cell. This knowledge will help us design strategies for killing CSCs by sensitizing them to DNA damage; for example, by targeting the preferred DNA repair system utilized by CSCs. We will also study how a protein complex named PBAF regulates the use of DNA repair machineries in CSCs. We chose the PBAF complex because its protein components are often mutated in tumors, and because others and we previously show PBAF facilitates repair of damaged DNA. In this work, we propose to generate a number of molecular tools, including a new type of cell derived from breast cancer, in which DNA damage can be induced throughout the whole genome. This will tell us when and where CSCs utilize one of the alternative DNA repair machineries to repair damaged DNA and how PBAF possibly changes the use of one machinery over the other. Overall, our results will help identify new targets for cancer diagnosis and spur the development of new therapies specifically directed against cancer stem cells.
01/01/2018	Richardson	Does Dietary Restriction Alter DNA Methylation in Intestinal Stem Cells?	Stem cells play an important role in the ability of tissues to repair themselves. Therefore, maintaining stem cell function could be important in preventing the decline health and function that occurs as we age. Dietary restriction retards aging and prevents the decline in physiological function. Dietary restriction also enhances the function of stem cells. Therefore, the anti-aging effect of dietary restriction could arise from its effect on stem cells. Currently, we do not know how dietary restriction improves stem cell function. Stem cell function can be regulated through changes in DNA methylation. Therefore, we propose that dietary restriction leads to changes in DNA methylation in stem cells. The changes in DNA methylation then lead to alterations in gene expression, resulting in improved stem cell function. The goal of this project is to collect preliminary data that will be used to obtain NIH funding. We will use the latest technology to measure DNA methylation in genome of intestinal stem cells from mice. First, we will determine if dietary restriction induces changes in DNA methylation at specific sites in the genome. Second, we will identify the genes that are potentially changed by DNA methylation. Third, we will develop and test novel mouse models that will allow us to block changes in DNA methylation induced by dietary restriction.
07/01/2017	Bhattacharya	Role of BMI1 in Cancer Stem Cells: A Metabolic Perspective	Many cancers prove deadly because they come back within a short period after treatment. Cancer stem cells (CSCs) that are not affected by treatment are the major reason for this. CSCs are a small fraction of cancer cells that depend on the mitochondria for energy production. They quickly expand back to reform tumors. Currently there are no treatment options to specifically target CSCs and prevent cancer recurrence. This is due to the poor understanding of how CSCs survive and behave

			within the tumors. We have recently found that the stem cell protein BMI1, by being present in the mitochondria and the nucleus regulates energy production and drug efflux. CSCs also depend on these factors for their survival. We and others have shown that ovarian cancer patients with low BMI1 levels in the tumor live longer, with lesser chances of recurrence. Based on this information, we hypothesize that BMI1 supports the survival and expansion of CSCs and reducing BMI1 levels might provide an effective roadmap to prevent resistance and conventional therapy failure. We have developed a model of ovarian cancer stem cell based system in which we will dissect the role of BMI1 in maintaining cancer stem cells and develop strategies to destroy these cells. Targeting BMI1 will hold the holy grail of the new age cancer stem cell based therapy for treating ovarian and other cancers that are plagued by frequent recurrence.
07/01/2017	Forsthoefel	Role of adult stem cells in digestive tract regeneration	In the human digestive tract, adult stem cells replace all of the cells that line the esophagus, stomach, small intestine, and colon every 3-5 days, in response to normal “wear and tear” caused by digestion of food and absorption of nutrients. However, these organs are very limited in their ability to repair damage caused by traumatic injury, diseases like colon cancer, or surgical removal required to treat disease. By contrast, some animals, like freshwater flatworms called planarians, can repair or even replace large portions of their digestive systems after injury or even complete amputation. Even after cutting a planarian into 10 pieces, each piece will regenerate into a perfectly normal animal, with a fully functional intestine, within two weeks. Similar to humans, planarians have adult stem cells; however, planarian stem cells are much better at responding to injury and regenerating damaged organs. In this proposal, we will use powerful new genetic technologies, called “functional genomics,” to quickly identify specific sets of genes that are required for planarian adult stem cells to repair the injured intestine. Since humans and planarians have many similar genes in their DNA, what we learn is likely to inform medical efforts to promote regeneration of damaged or diseased digestive organs in humans.
07/01/2017	Gorbsky	Identifying Novel Genes in Adult Tissue Regeneration	The ability of some lower animals such as amphibians to regenerate internal organs and external appendages is extraordinary. Extending this capability to humans would be among the most profound advances conceivable for medical research. Despite years of research analyzing these capabilities in amphibians and other animals, we are far from understanding the crucial molecular pathways involved. Combining bioinformatic identification of potential candidate genes with a revolutionary system to rapidly delete these genes in *Xenopus* frogs, this application proposes to identify novel pathways in adult tissue regeneration. Unlocking this capacity in human tissues would allow the body to repair itself, an ideal solution to a wide variety of human health issues such as spinal cord injury, heart attack, neurodegeneration, and traumatic limb loss. Frogs develop from tadpoles, which undergo metamorphosis to become adults. Frog tadpoles have extensive abilities to regenerate, but this ability becomes limited in the adult frog. To reactivate regeneration in humans, we need to determine the important genes whose products regulate this process. Dr. Jonathan Wren, a bioinformatics expert, has used computer analysis of publically available genetic data from thousands of experiments to predict genes whose expression are likely to be important in regeneration. We have taken the first steps in simplifying gene knockouts in the two most commonly used laboratory frog species, and we apply this novel technology to test potential regeneration genes. In this way, we will identify new pathways involved in the recruitment of adult stem cells for regeneration.
07/01/2017	Griffin T	Effect of obesity and aging on adult chondrocyte progenitor cells	Osteoarthritis is a major cause of disability as we age. It affects joints throughout the body, especially the knee. A central feature of osteoarthritis is the loss of articular cartilage, which is the smooth, rubbery tissue that cushions the ends of bones during movement. Obesity speeds up the loss of cartilage and causes pain that makes it even more difficult to exercise and lose weight. There are currently no treatments that slow down cartilage loss, which is especially needed with obesity. The long-term goal of this study is to learn how obesity and aging reduce the ability of cartilage to heal itself. The focus of this proposal is on the recently discovered adult stem cells (chondrocyte progenitor cells or CPCs) present in articular cartilage. These cells are located in the cartilage

			surface layer, and during aging, they give rise to new chondrocytes that produce cartilage-strengthening proteins. When a bone breaks, different adult stem cells travel through the blood to stimulate new bone growth. However, cartilage has no blood supply and relies only on CPCs for repair. We think that one way that obesity speeds up cartilage loss is by reducing the ability of CPCs to renew themselves and to give rise to chondrocytes that are needed for maintaining tissue structure. We will test this idea by tracking the number and function of CPCs in aging obese mice and high-fat CPC culture models that mimic aging. This research may lead to new treatments that preserve CPC function and delay cartilage loss.
07/01/2017	Olson L	PDGF signaling in Skeletal Stem Cells and Postnatal Bone Growth	Bones seem like fixed structures because they are hard and they persist long after death, but in fact they are surprisingly dynamic and undergo complete turnover 3-5 times between skeletal maturity and death. Also, bone fractures can heal, and in fact they heal more completely than injuries to most other tissues. The turnover and healing ability of bones is possible because they harbor adult skeletal stem cells (SSCs). These cells are sometimes called mesenchymal stem cells. SSCs reside inside bones where they are attached to the outer surface of blood vessels. SSCs are multipotent, meaning they can turn into different cell types for instance osteoblasts (bone forming cells), chondrocytes (cartilage forming cells), and adipocytes (fat cells). SSCs also exert control over hematopoietic stem cells that supply red and white blood cells throughout life. The field of regenerative medicine has been keenly interested in SSCs for decades, but there is still so much we do not understand about how they are regulated and how they might be used for therapy. The Olson laboratory studies a growth signal called platelet-derived growth factor (PDGF), which binds to PDGF receptors (PDGFRs) on the surface of many cell types. It was recently discovered that SSCs have PDGFRs, but the role of this growth signal has not been carefully studied in SSCs and adult skeletal biology. We have strains of mice with mutations that elevate the level of PDGFR signaling activity, and our preliminary data shows that this results in bone growth, changes in skeletal mineralization, and formation of bone marrow in unusual places like skull. These phenotypes suggest that PDGFR signaling is causing SSCs to behave abnormally in adult mice. The goal of this proposal is to develop a better understanding of which cells in the bone express PDGFR, what bone structures are derived from PDGFR expressing cells, and how PDGFR mutations change SSC function in adult bones and in a cell culture setting. These experiments will help us understand how PDGF regulates SSCs, which is important for developing SSC-based therapy.
07/01/2017	Srinivasan	Mechanical force induced differentiation of lymphatic endothelial cell progenitors	The mammalian lymphatic vasculature is vital for the return of tissue fluids to the circulating blood. It also absorbs digested lipids from the intestine. Abnormal functioning of the lymphatic vasculature causes swelling of body parts, especially the limbs. This is known as lymphedema, a common disorder that results from either mutations in genes that regulate lymphatic vascular development or more often from surgical damage to the lymphatic vessels and valves. Millions of humans are estimated to be suffering with lymphedema in the US alone. Currently, no cure is available for patients with lymphedema; therefore, only palliative treatments like massage are prescribed. Most of the tissues are thought to contain a few stem cells that function to repair mild to moderate tissue damage caused by aging. Efforts are ongoing to determine the identity of these adult stem cells and to enhance their ability to repair more severe tissue damage. We propose to define the mechanisms that control the differentiation of lymphatic progenitor cells into valves. Knowledge gained from our work might provide an opportunity to harness the potential of adult stem cells and treat lymphedema.
07/01/2017	Walters	Notch-mediated regulation of airway epithelial secretory cell differentiation	Chronic obstructive pulmonary disease (COPD) is the 3rd leading cause of death in the US. The disease is mostly caused by cigarette smoking, which damages the airways and lung. Currently, there is no cure for COPD or therapy to repair damage to the airways and lung. Epithelial cells line the airway providing a protective barrier to the outside world. Two types of epithelial cells that protect the airway are secretory and ciliated cells. Secretory cells produce a sticky substance called mucus, which helps trap foreign particles including bacteria and viruses from entering the lung. Ciliated cells have specialized structures called cilia, which function as a brush to help remove mucus from the

			airways. In response to damage, resident stem/ progenitor cells repair the airway epithelial cell layer by changing into the types of cells that need replacing in a process called “differentiation”. Cigarette smoking disrupts differentiation of the stem/progenitor cells, resulting in changes to the airway epithelial cell layer. One change includes increased numbers of secretory cells and decreased numbers of ciliated cells. The result of this change is production of excess mucus, which blocks the airways leading to breathing difficulties and increased lung infections. This has a significant negative impact on the health of people with COPD. Our study will give us a better understanding of how airway stem/progenitor cells become secretory cells. In turn, this will help the development of new stem cell based treatments to repair damage to the airways and treat people with COPD.
07/01/2017	Zhang	How Integrin Regulates the Adipogenesis of Mesenchymal Stem Cells	Fat tissues and fat cells are important for health, and abnormal formation and turnover of fat tissues and fat cells are associated with various diseases and/or susceptibility of diseases such as diabetes and heart diseases. After birth, fat cells are originated from a type of source cells called mesenchymal stem cells. How this type of stem cells becomes fat cells is still unclear. But understanding how this type of stem cells becomes fat cells and form fat tissue is quite important for us to change the formation and turnover of fat tissues in our bodies. Recently, we found that a group of candidate proteins can promote the formation of fat cells from their source cells, i.e., mesenchymal stem cells. In this study, we will find out exactly which one of these candidate proteins promotes the formation of fat cells. Then, we will figure out how this key protein promotes the formation of fat cells. From this study, we will likely discover an important regulator for the formation and turnover of fat tissues. This regulator will have a great potential to be clinically beneficial for disease intervention. The knowledge and conclusion from this study will also be significant for preventing various diseases as described above. Moreover, the outcome of our study will be very useful for cosmetic and fitness purposes.
01/01/2017	Freeman	Epigenome of Neural Stem Cells with Aging	The ability to learn and remember new tasks and facts declines with aging. This occurs even during normal aging where there is not significant loss of neurons in the brain. Previous studies have demonstrated that learning and memory require proper function of adult stem cells present in the brain and that these neural adult stem cells have impaired function with aging. Furthermore, studies have shown that restoring function of these adult stem cells improves learning and memory in older mice. However, the cause of this impaired function in the neural stem cells with aging remains unknown. Our hypothesis is that the epigenome, the modifications to the genome present in every cell that control the regulation and expression of genes, in these adult stem cells changes with aging, decreasing their ability to replicate and to secrete factors that promote proper brain function. Using new technologies that we have developed and optimized we can analyze the epigenome of isolated neural stem cells from young, adult and old mice (both males and females) to determine how the epigenome in these cells change with aging. By understanding how the epigenome changes in these neural stem cells with aging we can identify targets for development of drugs that restore a ‘youthful’ state to neural stem cells and improve learning and memory in older individuals.
01/01/2017	James	Using Circulating Progenitor Cells to Examine the Role of Stem Cell Factor (SCF) in SLE pathogenesis	Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by immune cell dysfunction. Recent research has identified that the protein stem cell factor (SCF) is increased in SLE patients compared to healthy controls, elevates in individuals immediately before clinical lupus develops, and is elevated in lupus patients right before their disease flares. SCF is a ligand that interacts with its receptor, c-kit (also called CD117). Previous research has shown that this interaction helps replenish stem cells that eventually become immune cells (hematopoiesis). Some immune cells that participate in the immune response (to fight infection or cause autoimmune disease) express c-kit/CD117 on their surface. SCF interacting with CD117 on immune cells triggers a pro-inflammatory response. Despite this knowledge, how SCF contributes to SLE and other autoimmune disease pathogenesis is unclear. This project will determine the ability of SCF to cause a proinflammatory response in immune cells from SLE patients compared to healthy individuals. We will also determine the ability of SCF to activate progenitor cells (stem cells in the blood that express CD117 and can become immune cells) and help them differentiate into immune cells in SLE patients

			compared to healthy individuals. Our findings will advance the field of stem cell biology, moving our understanding of stem cells and factors beyond cellular regeneration to their role in inflammation and autoimmune disease pathogenesis.
01/01/2017	Janknecht	Role of DNPH1 in Breast Cancer Stem Cells	Why does breast cancer often arise again after seemingly successful treatment? One reason is the presence of breast cancer stem cells (BCSCs) that evade conventional therapy and can lie dormant for many years before re-initiating tumor formation. Hence, finding ways to target BCSCs would greatly improve the cure of breast cancer patients. We believe that the DNPH1 enzyme could be a novel valid target to suppress BCSCs. First, we found that DNPH1 is required for efficient formation and metastasis of breast tumors. And second, we show that DNPH1 depletion also reduces the number of BCSCs. Based on these data, we will explore how DNPH1 affects properties of BCSCs (e.g. *in vitro* and *in vivo* growth) and attempt to define molecular mechanisms for DNPH1's action. For these experiments, we will utilize mouse BCSCs and those derived from adult human breast cancer cell lines. Altogether, the proposed research will provide valuable insights into the biology of BCSCs and hopefully point out that DNPH1 inhibition could be utilized to kill or suppress BCSCs. This has the potential to save thousands of lives every year in the US.
01/01/2017	Kovats	Differentiation of human hematopoietic stem cells to lung resident immune cells in a tissue-engineered lung model"	The global burden of disease caused by lung infection is significant in both poor and wealthy regions. Lung infections are increasingly life threatening due to the emergence of new types of viruses and bacteria, antibiotic resistance and growth of particularly susceptible populations (the very young and the elderly). Eliminating detrimental viruses and bacteria from the lung requires immune responses of lung cells, including "dendritic cells", which are the first line of immune defense against infection and also can promote asthma. Adult stem cells found in the blood that give rise to the immune system are also present in the human lung. Research with mice showed that these stem cells develop into dendritic cells. The number of stem cells that develop into dendritic cells increases during inflammation. However, the steps involved in this process within the human lung have not been well studied. We have built an artificial human lung model containing the diverse cells within normal human lungs. Here, we propose to use this "tissue-engineered" model to study how blood stem cells convert to dendritic cells of the immune system. This research will help us to understand how blood stem cells can convert into the mature immune system cells present in human lungs. The study will also help us to understand how inflammation caused by viral and bacterial infection might change how these blood stem cells develop into cells of the immune system. This new understanding will help in the development of new treatments for lung disease.
01/01/2017	Le	Stem Cell Characteristics of Muller Glia	Visual signals are formed by interconnected neurons that cannot be renewed or regenerated. Damages to these neurons by environmental or genetic insults cause vision loss, a leading disability in the United States. With the development of regenerative medicine, a major strategy to treat vision loss caused by neuronal degeneration is to replace the "bad" neurons with heathy ones obtained by regeneration from stem cells. Müller cells, which have adult stem cell characteristics, can be converted to neuron-like cells in the eye. While previous studies by many laboratories have demonstrated the possibility to renew Müller cells and to convert them into neuron-like cells, inducing Müller cell renewal has become a bottle neck that hampers Müller cell-derived neuronal regeneration significantly. Based on our preliminary data, we propose the following Specific Aims: 1) to study the mechanism of trophic factor-mediated Müller cell renewal, 2) to establish efficient methods to induce Müller cell renewal, and 3) to explore the stem cell function of Müller cells in neuroprotection in the eye. The data obtained in this study will give us a competitive position in this field.
01/01/2017	Mao	Efficiently reprogramming human fibroblasts into iPSCs by non-viral nanoparticles	Human induced pluripotent stem cells (hiPSCs) are desired compared to more traditional embryonic stem cells for disease treatments. This is because they can be obtained by conversion of a patient's own mature somatic cells by transferring reprogramming genes into the cells, a process called reprogramming, thus avoiding ethical limitations. To create hiPSCs, somatic cells are genetically reprogrammed, typically by using either a viral or non-viral vector. While non-viral methods can be safer, the conversion rates from somatic cells to hiPSCs are traditionally low (0.0001%-0.1%), usually lower than those resulting from the unsafe viral vectors (which can reach 1.5%). Our goal is to

			develop a highly efficient non-viral gene transfer approach to meet an increasing demand for hiPSCs. We propose to decorate lipid-based nanoparticles with peptides, which allow for the targeted delivery of both reprogramming genes and a new, highly efficient gene editing tool known as CRISPR/CAS9, to a type of somatic cell called a fibroblast. Once the fibroblast has been targeted, CRISPR/CAS9 will help to insert the reprogramming genes into a specific location in the genome, avoiding undesired random insertions. Then, the reprogramming genes will be efficiently translated into proteins, which function to convert fibroblasts into hiPSCs with improved rates. Preliminary data shows that nanoparticles modified by a cell targeting peptide show a significantly higher gene transfer efficiency when compared to an industry standard, Lipofectamine®2000. We hypothesize that utilizing both the targeted reprogramming gene delivery and powerful gene editing tool will greatly improve the nonviral reprogramming of somatic cells into hiPSCs.
01/01/2017	Rankin	Contributions of cohesin and condensin to nuclear reprogramming: and in vitro model for induced pluripotency	Stem cells are defined by two essential properties: first, they are able to make perfect copies of themselves, and secondly, when necessary they can develop into many different cell types, such as blood or nerve cells, in a process called “differentiation”. Differentiated cells in general have lost the ability to self-replicate and are committed to their specialized roles in the body. Something remarkable happens when the nucleus (in which all genes are packaged) from a differentiated cell is injected into an egg: it begins to acquire the properties of a stem cell nucleus. This is a process referred to as “reprogramming”. In some cases reprogrammed nuclei can even go on to make an entire organism, indicating that the transferred nucleus has become pluripotent, or able to make all tissue types. We are interested in the structural changes that occur during nuclear reprogramming. This proposal is a request for funding to continue experiments that were initiated during a prior funding cycle. In this cycle, we are adding exciting new live-cell imaging strategies to our approach. We continue to investigate how two protein machines, called Cohesin and Condensin, cooperate and promote the nuclear changes seen during reprogramming. The ultimate goal of such experiments is to understand reprogramming so that it can be manipulated for medical applications.
01/01/2017	Tanaka	Intratumoral Wound repair promotes the emergence of cancer stem cells	Cancer Stem Cells (CSCs) are an emerging problem in current cancer therapy. Resistant to both chemotherapy and radiotherapy, no existing therapeutic options are capable of eradicating CSCs. The origins of adult CSCs are not clearly understood; however, it is suggested that extrinsic stimuli support the acquisition of a stem-like phenotype to cancer cells. Our study focuses on the extrinsic mechanism of CSC property acquisition following biopsy. Our preliminary data indicated that a time to surgery of longer than 7 weeks after biopsy reduces survival among node-negative breast cancer patients. We hypothesized that wound repair following core needle biopsy results in the development of a reactive tumor stroma environment, which promotes the emergence of invasive mesenchymal feature and drug resistant CSCs. Therefore, prolonged exposure of naïve cancer cells to wound fluid from the reactive stroma confers a metastasis competent environment and consequently reduces overall survival in lymph node negative breast tumors. We aim to understand the mechanism underlying the emergence of CSCs following biopsy with the ultimate goal of establishing a measurable guideline for the allowable duration between biopsy and surgery.
7/1/2016	Gappa-Fahlenkamp	Using a Tissue-Engineered Vascular Model to Develop Mast Cells from Adult Stem Cells	Over the last few decades, the prevalence of allergic diseases has increased dramatically. Our long-term research goal is to create three-dimensional (3D) tissue-engineered models that can be used to study the immune response involved in allergic diseases. The tissue-engineered model consist of human mast cells and fibroblast cells within a 3D matrix that represents the tissue space and a layer of endothelial cells that line the blood vessels in the body. Mast cells play an important role in an allergic immune response; however, they are difficult to attain. Others have determined methods to grow large numbers of mast cells in traditional two-dimensional (2D) cell culture from various sources of adult stem cells. For the first time, we have shown that it is possible to grow mast cells from one type of adult stem cells in a 3D tissue-engineered model and that these cells are different than those generated from 2D cell culture systems. We believe that the tissue-engineered model can be used to develop mast cells from a variety of adult stem cell sources and that the cells are more functional than those developed in 2D cell culture systems due to the influence of the other cells types within the model. The

			outcomes of this project will lead to a better source of human mast cells and a new model that can be used to study allergic diseases and to test treatment strategies.
7/1/2016	Gorbsky	New Models for Tissue Regeneration	An ardent goal of medical science is enabling humans to regenerate internal and external body parts with high fidelity. Regeneration capabilities are extremely well developed in certain animals, particularly invertebrates such as starfish, octopus, and crab, which can regrow nearly all body parts. Certain vertebrates, including salamanders and fish, also exhibit extensive powers of regeneration. In humans, the liver has a strong ability to regenerate after it is damaged. Unlocking this capacity in other human tissues would allow the body to repair itself more easily, an ideal solution to a wide variety of human health issues such as spinal cord injury, heart attack, neurodegeneration, and traumatic limb loss. Frogs develop from tadpoles, which undergo metamorphosis to become adults. Frog tadpoles have extensive abilities to regenerate, but this ability is lost in the adult frog. To understand how to reactivate regeneration in humans, we need to determine the important genes that regulate this process. Dr. Jonathan Wren, a bioinformatics expert, has used computer analysis of publically available genetic data from thousands of experiments to predict genes whose expression may be important in regeneration. We have taken the first steps in simplifying genetic studies in the two most commonly used laboratory frog species. We will refine this novel technology and use it to test genes involved in regeneration. This revolutionary technology will also empower the ability of researchers to study many other biomedical questions with this powerful model system.
7/1/2016	Liu	Stem Cell-based therapy of Influenza virus Infection	There are 200,000 hospitalizations and 36,000 deaths each year in the US because of influenza virus infection, resulting in an enormous economic burden. Currently available anti-flu drugs target viral proteins. Influenza virus constantly changes and thus these drugs become ineffective. This research project explores the use of mesenchymal stem cells to treat influenza virus infection. The outcome of this project may lead to the new therapy for influenza virus infection.
7/1/2016	Sansam	DNA Replication Regulating Heterochromatin During Stem Cell Differentiation	Researchers can now transform virtually any mature cell type taken from a patient's body into an induced pluripotent stem cell (iPS), which has the capacity to differentiate into any type of cell in the body. This iPS technology is emerging as a personalized therapeutic treatment option for a wide range of diseases. A current problem in iPS cell technology is the inefficiency by which cells can be reprogrammed. Converting mature cells into iPS cells and *vice versa* involves repackaging the DNA into "chromatin" so that genes are appropriately silenced or activated. A gene called Rif1 was recently shown to be required for normal changes in chromatin structure that accompany stem cell differentiation. The genes and systems used by human cells are virtually identical to those used by simpler and more experimentally accessible vertebrates such as the zebrafish. The work proposed for this grant will use the zebrafish as a model system to define how the Rif1 gene causes changes in chromatin structure during stem cell differentiation. Ultimately, we expect that such knowledge will aid in the development of safe and efficient strategies for directed adult stem cell differentiation and reprogramming in humans.
7/1/2016	Srinivasan	Defining the mechanisms of Wnt/betacatenin signaling pathway in lymphovenous valve progenitors	The mammalian lymphatic vasculature maintains fluid homeostasis by returning tissue fluids to blood. Lymphatic vessels also absorb digested lipids from the intestine. Defects in the development of lymphatic vasculature results in a poorly understood disease called lymphedema. Swelling of body parts, especially the limbs, is one of the obvious symptoms of lymphedema. Elderly people are more prone to lymphedema. Thousands of people are suffering with lymphedema in the United States alone. Currently, no cure is available for patients with lymphedema; therefore, only palliative treatments like massage are prescribed. Critical to lymphatic vascular functioning are four valves that are located at the junction of lymphatic and blood circulations. We recently demonstrated that these valves are abnormal in multiple mouse models of lymphedema. Therefore, we believe that repairing these valves might correct lymphedema. Most of the tissues contain a few stem cells that function to repair tissue damage caused by aging. Efforts are ongoing to determine the identity of these adult stem cells and to enhance their ability to repair and even regenerate organs. We have identified a powerful signaling pathway that is necessary for the formation of the progenitors of the aforementioned valves. We propose to dissect the mechanisms of action of this pathway, as this will be an important step in developing stem cell- based treatments for lymphedema.

7/1/2016	Tsiokas	Role of the primary cilium in mesenchymal stem cell self-renewal and differentiation	Adult somatic stem cells are unique among other cell types because they can exist in a quiescent sate for long periods of time. However, under the right conditions, they can transit to a state of proliferation (self-renewal) and generation of multiple kinds of differentiated progeny (differentiation). Therefore, better understanding the cell biological and molecular mechanisms underlying these properties will have a great impact on our ability to utilize these powerful cells in regenerative medicine. The primary cilium is an antenna-like organelle present in most types of adult stem cells. Emerging evidence suggests that this tiny organelle houses the signaling machinery regulating quiescence, self-renewal and differentiation. We have discovered a cellular program that controls ciliary formation and function. Molecules within this program can be pharmacologically targeted allowing us to induce or suppress ciliogenesis. In this proposal, we want to test whether this program can affect specialized properties of stem cells, such as quiescence, self-renewal and differentiation. As a model system, we will use mesenchymal stem cells derived from the adult mouse bone marrow. These cells have a primary cilium and can give rise to numerous cell types, such as osteoblasts, chondrocytes, adipocytes, cells forming the tendons, and muscle cells. We hope that pharmacologic manipulation of the primary cilium and signaling pathways housed within this organelle could improve methods to culture and utilize adult stem cells for therapeutic purposes.
7/1/2016	Xia	Modulation of intestinal epithelial stem cells and their niches as a colitis therapy	Ulcerative colitis is an inflammatory disease that affects the large intestine with unknown cause and cure. The disease affects many people in the United States, leading too physical as well as psychological discomfort and even disability. The intestine, especially the large intestine (colon), is lined with a mucus layer composed of large sugar molecules called O-glycans. We found that the mucus functions as a fence to protect intestinal cells, especially intestinal stem cells. Genetically engineered mice lacking intestinal O-glycans exhibit spontaneous colitis (colon inflammation) and impaired intestinal stem cell function, both of which resemble the human disease. In this proposal, we will test 1) that the O-glycan-dependent mucus functions as a fence to provide a healthy niche for normal intestinal stem cell function, 2) the combination of a mucus repairing therapy with intestinal stem cell transplantation as a treatment for colitis using our unique O-glycans-lacking mouse colitis model. This study is innovative because it uses a novel mouse model and focuses on the intestinal stem cell transplantation therapy. The intestinal stem cell, like blood stem cells, represents a classic example of adult stem cells. We envision intestinal stem cell transplantation as proposed in this study will become an effective treatment, like bone marrow transplantation for many blood disorders, for intestinal diseases like colitis.
7/1/2016	Zhang	How Integrin Regulates the Adipogenesis of Mesenchymal Stem Cells	Fat tissues and fat cells are important for health, and abnormal formation and turnover of fat tissues and fat cells are associated with various diseases and/or susceptibility of diseases such as diabetes and heart diseases. After birth, fat cells are originated from a type of source cells called mesenchymal stem cells. How this type of stem cells becomes fat cells is still unclear. But understanding how this type of stem cells becomes fat cells and form fat tissue is quite important for us to change the formation and turnover of fat tissues in our bodies. Recently, we found that a group of candidate proteins can promote the formation of fat cells from their source cells, i.e., mesenchymal stem cells. In this study, we will find out exactly which one of these candidate proteins promotes the formation of fat cells. Then, we will figure out how this key protein promotes the formation of fat cells. From this study, we will likely discover an important regulator for the formation and turnover of fat tissues. This regulator will have a great potential to be clinically beneficial for disease intervention. The knowledge and conclusion from this study will also be significant for preventing various diseases as described above. Moreover, the outcome of our study will be very useful for cosmetic and fitness purposes.
1/1/2016	Carr	HSV-1 and Corneal Innervation	Herpes simplex virus type 1 (HSV-1) is a cause of neurotrophic keratitis (NTK), a degenerative disease characterized by decreased corneal sensation, blink reflex and tear secretion as a consequence of damage to the sensory fibers innervating the cornea. We have found during the acute phase of infection, HSV-1 causes retraction of the corneal nerves with loss of corneal sensitivity that is prevented by topical treatment with the anti-inflammatory drug, dexamethasone. Of the nerves remaining, we have discovered neural stem cells (NSC)/progenitor cells are associated with them. Moreover, unlike other studies, we have discovered the nerves re-innervate the cornea proper following resolution of the virus and such nerves are associated with the NSC. However, the tactile function of the re-innervated cornea does not recover. As a result of a previously funded OCASCR application, we have identified candidate cells and factors that contribute to HSV-1-driven de-

			innervation. In the present proposal, we would like to characterize the primary factors that drive de-innervation, signaling pathways involved, and cell source of the de-innervating molecules. In addition and pertinent to the theme of stem cell biology, we would like to interrogate the NSC gene profile prior to and after infection as it is our hypothesis the NSC is responsible for the re-innervation of the cornea during the recovery phase following virus clearance. The data and papers generated from the proposed study will greatly enhance our desire to secure NIH funding and further pursue the role of cornea NSC in response to infection, trauma, and diabetes.
1/1/2016	Le	Stem cell characteristics of Müller glia	Visual signals are formed by interconnected neurons that cannot be renewed or regenerated. Damages to these neurons by environmental or genetic insults cause vision loss, a leading disability in the United States. With the development of regenerative medicine, a major strategy to treat vision loss caused by neuronal degeneration is to replace the “bad” neurons with heathy ones obtained by regeneration from stem cells. Müller cells, which have adult stem cell characteristics, can be converted to neuron-like cells in the eye. While previous studies by many laboratories have demonstrated the possibility to renew Müller cells and to convert them into neuron-like cells, inducing Müller cell renewal has become a bottle neck that hampers Müller cell-derived neuronal regeneration significantly. In this application, we propose 1) to study the mechanism of Müller cell renewal, 2) to establish more efficient methods to induce Müller cell renewal, and 3) to explore the stem cell function of Müller cells in neuroprotection in the eye. The data obtained in this study will give us a competitive position in this field.
1/1/2016	Olson	Control of Mesenchymal Progenitor Cell Fate in Tissue Fibrosis	Fibrosis is a disease process where normal cells become pro-fibrotic, leading them to generate excess collagen that replaces functional tissues. This is a major pathological feature of heart disease and atherosclerosis, numerous autoimmune diseases, end-stage liver disease, and kidney failure. We need to understand the core mechanisms of fibrosis because we lack treatment strategies that specifically target the fibrogenic process in most diseases. From what is known, fibrosis occurs when resting connective tissue cells become activated to make excessive collagen. These connective tissue cells come from mesenchymal progenitor cells (MPCs). My laboratory is trying to understand the genetic mechanisms that cause MPCs to become activated connective tissue cells. This understanding will give us insight into what approaches might be useful to stop fibrosis. This proposal has two parts. In the first part we are focusing on a series of enzymes that work together to transmit signals from the cell surface to the DNA. This is called a signaling pathway. We hypothesize that the PI3K/Akt/mTOR signaling pathway is important for activated connective tissue cells to arise from MPCs. In the second part of the proposal we are continuing the previous year’s work on a new protein called Trnp1, which binds to DNA and regulates gene expression. We hypothesize that Trnp1 is needed for activated connective tissue cells to arise from MPCs. Our experiments will use MPCs isolated from mice, which can be grown in plastic dishes and manipulated with drugs or viruses to activate or block the PI3K/Akt/mTOR pathway, or to change the levels of Trnp1 in the cell. The modified MPCs can then be studied in plastic dishes or transplanted back into mice to study how they behave differently from normal MPCs. These experiments will help illuminate the core mechanisms of fibrosis.
1/1/2016	Pezza	The Role of Chromatin Remodeling Complexes in the DNA Damage Response of Cancer Stem Cells.	Recent advances in cancer biology have suggested that a specific subset of cancer cells, cancer stem cells, can regenerate a tumor even after initial efficient anti-cancer therapies. Therefore, targeting this population of cancer cells is an important step forward in cancer treatment. We are focusing our studies on understanding the repair of DNA double strand breaks (DNA damage), which are induced by current therapies to specifically induce cancer cell death, in a novel cultured-base model of cancer stem cells (BPLER cells). Interestingly, stem cells have been suggested to preferentially utilize the homologous recombination pathway to repair DNA double strand breaks for unknown reasons. Therefore, it is possible that cancer stem cells evade or resist current treatments by preferential utilization of the homologous recombination pathway. Further, we will determine the role of the PBAF chromatin-remodeling complex in DNA damage signaling and DNA repair. Recent reports and our preliminary results show that chromatin-remodeling complexes are required for the DNA repair machinery to access to DNA breaks, thus facilitating DNA repair. We hypothesize that alterations in the DNA repair pathways and/or epigenetic regulation of DNA repair through PBAF are the root causes of cancer stem cells resistance to therapy and tumor relapse. Understanding how cancer stem cells repair damaged DNA will help identify new targets for diagnosis and spur the development of new therapies specifically directed against cancer stem cells.
1/1/2016	Rankin	Contributions of Cohesin and	Stem cells are defined by two essential properties: first, they are able to make perfect copies of themselves, and secondly, when necessary they can develop into many different cell types, such as blood or nerve cells, in a

		Condensin to nuclear reprogramming: an in vitro model for induced pluripotency	process called “differentiation”. Differentiated cells in general have lost the ability to self-replicate and are committed to their specialized roles in the body. Something remarkable happens when the nucleus (in which all genes are packaged) from a differentiated cell is injected into an egg: it begins to acquire the properties of a stem cell nucleus. This is a process referred to as “reprogramming”. In some cases reprogrammed nuclei can even go on to make an entire organism, indicating that the transferred nucleus has become pluripotent, or able to make all tissue types. We are interested in the structural changes that occur during nuclear reprogramming. We have a system in which these changes can be induced in a test tube using frog egg extracts. This proposal is a request for funding to continue experiments that were initiated during a prior funding cycle. We plan to extend our preliminary results to better understand how two protein machines, called Cohesin and Condensin, cooperate and promote the nuclear changes seen during reprogramming. The ultimate goal of such experiments is to understand reprogramming so that it can be manipulated for medical applications.
1/1/2016	Tanaka	Intratumoral Wound Repair Promotes the Emergence of Cancer Stem Cells	Cancer Stem Cells (CSCs) are an emerging problem in cancer therapy today. CSCs are resistant to chemotherapy and radiotherapy, and therefore unfortunately there is no therapeutic option to eradicate CSCs. The origins of adult CSCs are not clearly understood; however it is suggested that extrinsic stimuli supports the acquisition of stem-like phenotype to cancer cells. Our preliminary data indicated that tumor acquires CSC phenotype shortly after the tumor is wounded in mouse model of breast cancer. A diagnostic needle biopsy is the first step that tumor is injured by external force and is a procedure that almost all breast cancer patients receive for definitive diagnosis. Our hypothesis is that a needle biopsy wound within the tumor and neighboring tissue predisposes acute inflammation and EMT that will result in the development of a reactive tumor stroma that subsequently causes an emergence of CSCs which may compromise the therapeutic efficacy of chemotherapy due to their chemo-resistant nature. We aim to understand the mechanism of the emergence of CSCs with an ultimate goal of the implementation of post-biopsy care for the prevention of the emergence of CSCs.
1/1/2016	Zenewicz	Establishment of a human ILC3 culture system from CD34+ stem cells	In this application, we will learn to grow a specific type of human immune cell starting with human stem cells. The human immune cells we are interested in are called ILC3s, which stands for group 3 innate lymphocytes (ILC3s). These are newly discovered cells that are important at mucosal barriers and help fight infections. These cells are very rare and it is difficult to obtain large numbers of them. In this project, we will isolate human stem cells from discarded tonsils and then culture these cells under special conditions to generate large numbers of ILC3s. At the end of the culture, we will check that the stem cells have properly turned into ILC3s. We will then develop an animal model to study the cells in an intact organism. We will inject the cultured ILC3s into mice that lack these cells and then determine if the cells can survive and thrive in the mouse. These studies will generate preliminary data for a future grant application to the National Institutes of Health.
07/1/2015	Humphrey	Targeted epigenetic modification to induce pluripotent gene expression	Induced pluripotent stem cells (iPS cells) have become a mainstay of scientific laboratories and discoveries since their intial development nearly a decade ago. Although they have immense basic research potential, the technology whereby they are generated has remained largely unchanged. It remains a difficult, time-intensive and notoriously inefficient process. Presently, the yield of iPS cells averages less than 5% with modern techniques. Converting “normal” cells to iPS cells requires the indirect alteration of the epigenetic state of a few key genes, a relatively infrequent event, likely contributing to low conversion efficiencies. In this project, we propose to circumvent this process and alter the epigenetic state of these genes directly, leveraging a novel modular protein system recently developed in our laboratory. This modular system allows for the targeting of enzymes that alter epigenetic marks to specific sites within the genome, effectively “turning on” these genes for an extended period of time following a single administration of the enzyme. Our previous experience has indicated that, using this method, we can achieve significant and long-lasting upregulation of individual genes with quite high efficiencies.
07/1/2015	Jones	Retinoic Acid Regulation of Intestinal Stem Cell Fating	Like most cancers, colon cancer begins from a series of genomic perturbations. A leading cause of colon cancer is the loss of adenomatous polyposis coli (APC) tumor suppressor. APC loss causes malfunction of WNT/ß-catenin signaling. These two events cause intestinal cells to remain in an immature state. This immature state then signals the start of colon cancer. Recently, our lab demonstrated an unexpected link between APC and DNA demethylases (DMs). We demonstrated that APC modulates retinoic acid (RA) levels. The loss of RA results in up regulation of DMs that direct intestinal cells to stay in an immature state. This finding suggests a novel role for APC in directing intestinal stem cell fate. Our data also suggest that RA controls intestinal inflammation. Based on these findings, we think that RA influences intestinal homeostasis in two ways. One, RA induces intestinal stem

			cell maturation by chromatin regulation in the epithelium. Two, RA controls the inflammatory cytokine balance by preventing Treg to TH17 differentiation outside the epithelium; this modifies the epithelial cell microenvironment and indirectly affects intestinal cell fating. These studies propose *a* new mechanism by which loss of *APC/RA* governs intestinal stem cell regeneration and fating.
07/1/2015	Liu	Mesenchymal Stem Cell Exosomes for Treating COPD	Chronic obstructive pulmonary disease (COPD) is a chronic lung disease. It is the fourth leading cause of death and affects over 16 million people in the USA. The major risk factor for COPD is cigarette smoking. There is no cure for COPD. The current treatment of COPD is palliative, with the goal of reducing symptoms and limiting recurrent exacerbations. The present proposal for adult stem cell therapy is intended to use exosomes derived from mesenchymal stem cells to treat COPD. The success of this approach would therefore represent significant progress towards a cure for COPD.
07/1/2015	Mao	Seeking peptides capable of inducing neural differentiation of human iPSCs	Induced pluripotent stem cells (iPSCs) have emerged as the best cell source for generating mature neurons, which are highly demanded in treating neurological diseases. Their use avoids the problems of immune rejection and ethical issue faced by other stem cells. However, one major challenge for clinical application of iPSCs is the lack of small inducer molecules that can efficiently guide their differentiation into specific desired cell type. This project aims to discover small molecules that can induce the neural differentiation of iPSCs, namely, the conversion of iPSCs only into neurons. Basic fibroblast growth factor (bFGF) is a well-documented large protein known to induce the neural differentiation of stem cells. However, it is expensive, has a short half-life and can cause side effects when inside the body. We hypothesize that a short segment (called peptide) can be picked out of bFGF for inducing the neural differentiation of iPSCs as efficiently as the whole bFGF protein. To prove this hypothesis, we will divide the entire sequence of human bFGF into 13 peptides based on their reported functions and structures and present them on human-safe tiny fibers (called phage) by genetic means, which are further orderly assembled into substrates for supporting iPSCs growth. The use of phage enables us to vary the peptides on the substrate with a constant architecture. The neural differentiation is verified by detecting the marker proteins unique for the formation of neurons. This project will discover single or dual peptide inducers that can most efficiently convert iPSCs into neurons.
07/1/2015	Naash	Dedifferentiation of Müller Glia into Retinal Progenitors could restore vision in models of retinal diseases	Vision loss is among the top ten disabilities in the United States, which results in a heavy financial burden on society. To remedy this problem, significant interest in recent years has been focused on the ability to regenerate neurons and neural connections in the eye and visual system (http://www.nei.nih.gov/audacious/). To accomplish this audacious goal, it is necessary to identify the molecular signals needed to “activate latent endogenous cells to replace lost host neurons”. In this application, we plan to translate in mouse retina what we know from other studies, in which retinal damage stimulates Müller glia to proliferate and produce neuronal progenitors that regenerate the missing neurons. While the mammalian retinas (mouse and human) also possess Müller glia, they are unable to regenerate retinal neurons. Therefor injecting in the mouse retina the molecular switches that are known to induce zebrafish Müller glia to initiate the regeneration response may identify approaches to induce a similar retinal regeneration response in mouse and human retinas. In this application, we plan to work with tumor necrosis factor alpha (TNFα) and notch signaling, both of which have recently been shown to act as regulators of Müller glia proliferation in zebrafish. We plan to elucidate the signaling pathways downstream of these two regulators to help develop strategies to regenerate retinal neurons in individuals who suffer from a variety of forms of blindness. Results from this study will help develop strategy to induce adult Müller cells in patients to replace the dying photoreceptors and restore vision.
07/1/2015	Sun	Eradicating CML by targeting cancer stem cells	Chronic myelogenous leukemia (CML) is one type of leukemia accounting for 20% of newly diagnosed adult leukemia cases. Although drugs are currently available to slow the disease by inhibiting the protein responsible for the growth of leukemic cells, patients often develop resistance to the drugs and progress to terminal stages. In addition, patients have to take the drug(s) for the rest of their lives once they are diagnosed and this poses an enormous financial burden as it costs approximately $100,000 per year. The reason for the need of continuous treatment and the development of drug resistance is that current therapies do not target the root of the disease, namely leukemic stem cells. Although the drugs kill the bulk of leukemic cells, new ones can always grow out from the stem cells. We have found a protein called Asb2 that is capable of destroying the proteins important for the survival and expansion of the leukemic stem cells. When Asb2 is produced in the blood cells, it hindered the development of CML in mouse models. We now need to test if Asb2 does so by impairing the stem cells.

			Furthermore, we are searching for drugs that can turn on the Asb2 gene in patients with CML, which may lead to the elimination of leukemic stem cells and the cure of CML.
07/1/2015	Tsiokas	Role of the primary cilium in mesenchymal stem cell self-renewal and differentiation	Adult somatic stem cells are unique among other cell types because they can exist in a quiescent sate for long periods of time. However, under the right conditions, they can transit to a state of proliferation (selfrenewal) and generation of multiple kinds of differentiated progeny (differentiation). Therefore, better understanding the cell biological and molecular mechanisms underlying these properties will have a great impact on our ability to utilize these powerful cells in regenerative medicine. The primary cilium is an antenna-like organelle present in most types of adult stem cells. Emerging evidence suggests that this tiny organelle houses the signaling machinery regulating quiescence, self-renewal and differentiation. We have discovered a cellular program that controls ciliary formation and function. Molecules within this program can be pharmacologically targeted allowing us to induce or suppress ciliogenesis. In this proposal, we want to test whether this program can affect specialized properties of stem cells, such as quiescence, self-renewal and differentiation. As a model system, we will use mesenchymal stem cells derived from the adult mouse bone marrow. These cells have a primary cilium and can give rise to numerous cell types, such as osteoblasts, chondrocytes, adipocytes, cells forming the tendons, and muscle cells. We hope that pharmacologic manipulation of the primary cilium and signaling pathways housed within this organelle could improve methods to culture and utilize adult stem cells for therapeutic purposes.
07/1/2015	Xia	Function of mucus layer in the intestinal stem cell niche	Hematopoietic stem cells (HSCs) generate all blood cell types during our lives. They need to carefully balance proliferation and differentiation to preserve themselves (self-renew), while generating enough blood cell precursors. Changes in this balance cause problems in human health. Age and chronic inflammation alter their potential to generate all blood lineages, while defects in their proliferation control cause many blood cancers (leukemias). We need to understand how HSCs regulate their proliferation and differentiation to manipulate these cells. This is relevant to treat the problems discussed above, as well as to improve our ability to manipulate HSCs with therapeutic purposes. In this proposal we will analyze the role of the protein c-Myb in regulating HSC function. It is known that HSCs need c-Myb to survive during adult life, but the mechanisms that underlie c-Myb function are not well understood. We will generate mice that express mutants of c-Myb that alter its ability to interact with different regulators to study in detail how c-Myb regulates HSCs. We will also directly test the interactions of c-Myb with Bmi1, a chromatin regulator known to be important in the control HSC function. These experiments will increase our understanding of HSC function and our ability to manipulate them. Furthermore, since c-Myb alterations play a role in human cancer, knowledge derived from these experiment could open new avenues for the treatment of some leukemias.
1/1/2015	Alberola-Ila	Role of c-Myb in LT-HSC homeostasis and function	Hematopoietic stem cells (HSCs) generate all blood cell types during our lives. They need to carefully balance proliferation and differentiation to preserve themselves (self-renew), while generating enough blood cell precursors. Changes in this balance cause problems in human health. Age and chronic inflammation alter their potential to generate all blood lineages, while defects in their proliferation control cause many blood cancers (leukemias). We need to understand how HSCs regulate their proliferation and differentiation to manipulate these cells. This is relevant to treat the problems discussed above, as well as to improve our ability to manipulate HSCs with therapeutic purposes. In this proposal we will analyze the role of the protein c-Myb in regulating HSC function. It is known that HSCs need c-Myb to survive during adult life, but the mechanisms that underlie c-Myb function are not well understood. We will generate mice that express mutants of c-Myb that alter its ability to interact with different regulators to study in detail how c-Myb regulates HSCs. We will also directly test the interactions of c-Myb with Bmi1, a chromatin regulator known to be important in the control HSC function. These experiments will increase our understanding of HSC function and our ability to manipulate them. Furthermore, since c-Myb alterations play a role in human cancer, knowledge derived from these experiment could open new avenues for the treatment of some leukemias.
1/1/2015	Gaffney	Induced Pluripotent Stem Cells to Understand Influence of BLK Variants on Early B Cell Function	Systemic lupus erythematosus (SLE) is a complex human disease characterized by immune cell dysfunction. Recent research has identified a number of genes associated with the development of SLE. One of these genes, *BLK*, plays a large role in the development of B cells, important immune system cells that protect against infections and help maintain a balanced immune system. Mutations in the *BLK* gene have been found to be associated with the development of SLE. This project will use stem cells made from previously isolated adult SLE

			patient blood cells to create a variety of B cells. These cells will then be used to examine differences in cell development and function caused by mutations in the *BLK* gene.
1/1/2015	Olson	A novel regulator of fibro-adipogenic fate of mesenchymal stem cells.	Fibrosis is a common and insidious disease process that progressively replaces functional tissue with collagen-rich scar tissue. All organs in the human body can be damaged by fibrosis, which leads to permanent scarring, organ dysfunction, and often death. For instance, scleroderma is an intractable autoimmune disease where scar tissue formation in the skin and internal organs leads to death. During obesity, fat tissue becomes fibrotic and contributes to insulin resistance and type-2 diabetes. Heart, liver, and kidney failure all occur in conjunction with irreversible scar tissue formation in the respective organs. There is a need for better understanding of the mechanisms of fibrosis because we lack treatment strategies that stop the formation of scar tissue. From what is known, fibrosis occurs when resting connective tissue cells become activated to make excessive collagen. These connective tissue cells come from mesenchymal stem cells (MSCs). My laboratory is trying to understand the genetic mechanisms that cause MSCs to become activated connective tissue cells. This understanding will give us insight into what approaches might be useful to stop fibrosis. In this proposal, we are focusing on a new gene called Trnp1, which binds to DNA and regulates gene expression. Our preliminary bioinformatic analyses show a strong correlation between Trnp1 being present in a cell and the cell making lots of collagen. Experiments in this proposal will test whether this relationship is causal, and will open the door to exploring what important fibrosis genes are regulated by Trnp1. We will also generate a new type of mouse strain where Trnp1 can be inactivated in adult mice. This mouse strain will allow us to eventually test the mice with challenges that should cause fibrosis, to see if inactivation of Trnp1 makes them resistant to fibrosis.
1/1/2015	Sansam	The Role for DNA Replication Timing in Determining Cell Fate In Vivo	Researchers can now transform virtually any mature cell type taken from a patient's body into an induced pluripotent stem cell (iPS), which has the capacity to differentiate into any type of cell in the body. This iPS technology is emerging as a personalized therapeutic treatment option for a wide range of diseases. A current problem in iPS cell technology is the inefficiency by which cells can be reprogrammed. Many changes occur during the reprogramming of mature cells, so an important question is: which changes are essential and rate limiting? One distinct change in cells as they differentiate is in the order and timing that different portions of the genome undergo replication. Each cell type has a characteristic DNA replication timing profile, and the replication timing profiles of stem cells differ substantially from those of mature differentiated cells. The biological function of this replication timing program is unknown. A gene called Rif1 was recently shown to be required for normal DNA replication timing. We will test whether control over replication timing is essential for stem cell differentiation, by examining the effects of Rif1 knockout in cells as they transform from an early embryonic state to mature somatic cells in zebrafish embryos. The identification of genes and processes essential for stem cell differentiation and reprogramming is a crucial step in developing novel stem cell therapies.
1/1/2015	Srinivasan	Coup-TFII and its cofactors in the specification of lymphatic endothelial cell progenitors	The lymphatic vasculature returns plasma fluids back to the blood circulation. Lymphatic vessels also collect digested lipids from the intestine and mediate immune surveillance. Damage to lymphatic vessels results in a deforming and debilitating disease known as lymphedema. In addition to causing swelling in the limbs lymphedema also causes inflammation, obesity, hypertension and in some cases a deadly form of blood vessel cancer known as angiosarcoma. Surgical damage to lymphatic vessels causes lymphedema in 20-30% of breast cancer survivors and only palliative treatments like massage and compression bandages are currently available. Millions of women suffer with lymphedema in the US alone and these numbers are expected to rise. Our longterm goal is to identify the mechanisms that give rise to progenitor cells of lymphatic vessels. This knowledge together with emerging stem cell technologies will be useful to repair damaged lymphatic vessels. With this goal we will identify the mechanisms of action of three molecules that play critical roles in the formation of lymphatic progenitor cells.
1/1/2015	Zhang	Tetraspanins Regulate Cancer Progression by Altering Cancer Stem Cells	Because cancer metastasis is the major cause of death for the patients with cancer, blocking cancer metastasis is crucial for the success of cancer treatment. A group of proteins called tetraspanin regulate cancer metastasis. Some tetraspanins ("bad ones") promote cancer metastasis, while others ("good ones") block cancer metastasis. Thus, tetraspanins can be used for the diagnosis and treatment of cancers. But, we still do not know how tetraspanins promote or block cancer metastasis. Recently, we found that tetraspanins can either expand or shrink cancer stem cell population. Interestingly, "good" tetraspanins shrink cancer stem cell population while "bad" tetraspanins expand cancer stem cell population. Whether tetraspanins regulate cancer metastasis by

			altering cancer stem cells becomes an obvious and important question. From this project, we would like to know whether or not cancer stem cells are crucial for 1) the blocking effect of “good” tetraspanins on cancer metastasis and 2) the promoting effect of “bad” tetraspanins on cancer metastasis. We will also determine how tetraspanins change the quantity and/or quality of cancer stem cell. The knowledge and conclusion from this study will 1) provide important insight into cancer therapy and 2) develop new strategy or medicine against cancer metastasis.
7/1/2014	Carr	HSV-1 and Corneal Innervation	Herpes simplex virus type 1 (HSV-1) is the leading cause of infectious corneal blindness in the industrialized world. At the Dean McGee Eye Institute in Oklahoma City, nearly 25% of all cases seen by ophthalmologists specializing in the cornea are due to HSV-1 infection. In addition to a loss in visual acuity, patients that suffer from HSV-1 infection lose sensation of the cornea resulting in a loss of blink reflex, and drying of the cornea. The cornea is the most innervated tissue in the body. In patients and in experimental animal studies, HSV-1 results in the regression of nerves that reside in the cornea. In our mouse model system, we have also found nerves regress during acute HSV-1 infection in the cornea. Of the nerves remaining, we have discovered neural stem cells (NSC)/progenitor cells are associated with them. Moreover, unlike other studies, we have discovered the nerves re-innervate the cornea proper following resolution of the virus and such nerves are associated with the NSC. Our hypothesis is the NSC are necessary to retain modest innervation during inflammation and contribute to re-innervation following ill-defined, inflammatory resolution. Presently, we do not understand the relationship between the NSC and existing nerves or the role the NSC have during and after HSV-1 infection. As de-innervation is a relatively common phenomenon in tissue as a result of inflammation due to trauma, ischemia, or autoimmunity, we believe the outcome of our proposed study has a broad spectrum of clinical applications.
7/1/2014	Gorbsky	Targeting Stem Cells in Cancer	Patients undergoing cancer treatment often show a strong initial response with regression of the tumor followed by a disease-free period. Sadly, this remission is often followed by resurgence of therapy-resistant tumors. The cancer stem cell theory suggests that tumors reappear because current treatments are designed to kill rapidly dividing tumor cells that make up the bulk of tumors but fail to target the cancer stem cells that grow more slowly but cause the relapse. Researchers have been looking for ways to target cancer stem cells so that they can be killed along with the bulk tumor cells at the time of initial treatment. Dr. Jonathan Wren, our bioinformatics collaborator, has used computer analysis of publicly available genetic data from thousands of experiments to predict genes whose expression is essential for proliferation of cancer stem cells. Using a new human breast cell line that contains a very high proportion of cancer stem-like cells, we have developed reliable growth assays and tested set of targets. We have obtained positive results suggesting that this approach can successfully identify novel breast cancer stem cell targets. We seek to continue this study to corroborate our initial hits, to identify as many more as possible and to determine the cellular pathways where the most potent hits participate. The identification of essential cancer stem cell genes and placing them in specific biochemical pathways are crucial steps toward design of drugs that can target cancer stem cells in primary cancer therapy.
7/1/2014	Gorbsky	Equipment-Upgrading Cell Dynamics Microscope	The Cell Dynamics Microscope for Live Cell Fluorescence is a highly advanced, multi-user, light microscope workstation constructed in 2005. Housed within the Cell Cycle and Cancer Biology Program at OMRF, it was established through a grant of $413,592 awarded in 2004 from the National Institutes of Health through the Shared Instrumentation Program. The application included projects from 5 major users and 9 minor users at OUHSC and OMRF. Dr. Gary Gorbsky spearheaded the application and remains director. The Cell Dynamics Microscope allows users to manipulate biochemical events in living cells and small organisms using light, and then observe the effects of these manipulations at very high resolution. Through its ten years of existence the workstation has undergone repair and upgrade of the optical system through funds provided by OMRF. Recent technical breakthroughs have resulted the release of a new generation of scientific grade digital cameras that open the opportunity for a significant upgrade in the speed and sensitivity of image acquisition of the instrument for a relatively modest investment. To accommodate this new camera and software upgrades, a new system computer for the system is needed. It is also necessary to replace our current, obsolete, off-line computer that allows us to process completed experiments while new experiments are underway on the workstation. The upgraded instrument will aid in carrying out current OCASCR-funded adult stem cell studies in the Gorbsky, Rankin, and Sansam laboratories in addition to it being available for other researchers.

7/1/2014	Jones	Retinoic Acid Regulation of Intestinal Stem Cell Fating	Like most cancers, colon cancer begins from a series of genomic perturbations. A leading cause of colon cancer is the loss of adenomatous polyposis coli (APC) tumor suppressor. APC loss causes malfunction of WNT/ß-catenin signaling. These two events cause intestinal cells to remain in an immature state. This immature state then signals the start of colon cancer. Recently, our lab demonstrated an unexpected link between APC and DNA demethylases (DMs). We demonstrated that APC modulates retinoic acid (RA) levels. The loss of RA results in up regulation of DMs that direct intestinal cells to stay in an immature state. This finding suggests a novel role for APC in directing intestinal stem cell fate. Our data also suggest that RA controls intestinal inflammation. Based on these findings, we think that RA influences intestinal homeostasis in two ways. One, RA induces intestinal stem cell maturation by chromatin regulation in the epithelium. Two, RA controls the inflammatory cytokine balance by preventing Treg to TH17 differentiation outside the epithelium; this modifies the epithelial cell microenvironment and indirectly affects intestinal cell fating. These studies propose a new mechanism by which loss of APC/RA governs intestinal stem cell regeneration and fating.
7/1/2014	Le	Stem cell characteristics of Müller glia for retinal neuron survival in diabetes	The retina is a light-sensitive tissue with several layers of interconnected neurons that are responsible for processing chemical and electrical inputs to form visual images in the brain eventually. In mammals, these retinal neurons cannot be renewed or regenerated after the damages induced by environment or genetic insults. Consequently, acquired and inherited retinal degenerations occur, such as that in diabetic retinopathy (DR), the number one cause of blindness in working age Americans. DR is a disease with dysfunctional vessels and degenerative neurons. While there is a general strategy to treat diabetes induced dysfunction of retinal vessels, surprisingly little is known about the mechanism and therapeutics for retinal neuron degeneration in DR. The focus of this OCASCR seed grant application is to investigate the potential of an adult retinal stem cell, Müller cell, in preventing retinal degeneration. In this study we will 1) investigate the mechanism of Müller cell renewal, 2) establish a procedure to induce Müller cell regeneration, 3) examine the effect of Müller cell renewal on neuro-protection in DR, and 4) explore the stem cell function of Müller cells in generating retinal neurons. The data obtained in this study will give us a competitive position in this field.
7/1/2014	Liu	Mesenchymal Stem Cell-Derived Lung Epithelial Cells for COPD Therapy	Chronic obstructive pulmonary disease (COPD) is a chronic lung disease. It is the fourth leading cause of death and affects over 16 million people in the USA. The major risk factor for COPD is cigarette smoking. There is no cure for COPD. The current treatment of COPD is palliative, with the goal of reducing symptoms and limiting recurrent exacerbations. The present proposal for adult stem cell therapy is intended to engineer mesenchymal stem cells with microRNAs for effective repairing or replacing damaged lung tissue in COPD. The success of this approach would therefore represent significant progress towards a cure for COPD.
7/1/2014	Lloyd	Adult stem cells to enhance repair of lung vasculature in chronic obstructive pulmonary disease	Chronic obstructive pulmonary disease (COPD) is a common chronic lung disease for which current treatments can only reduce symptoms, not provide a cure. Damage to endothelial cells of lung capillaries occurs in COPD and contributes to impaired oxygen exchange in these patients. Mesenchymal stem cells (MSC) are a type of adult stem cell that is naturally found in association with blood vessels. Furthermore, the beneficial effects of MSC have been reported to be at least partly due to production of vascular endothelial growth factor (VEGF-A), an important growth and survival factor for vascular endothelial cells. However, VEGF-A activates two different receptors (VEGFR-1 and VEGFR-2). Although VEGFR-2 activation is generally considered to be beneficial, VEGFR-1 activation is strongly implicated in inflammatory responses and appears to play a major role in the pathogenesis of COPD. Therefore, activation of both receptors may limit beneficial effects of VEGF-A. We propose to engineer MSC to produce and secrete a VEGFR-2 selective ligand. We hypothesize that increased VEGFR-2 activation induced by these engineered MSC and/or their conditioned medium will result in improved therapeutic efficacy in COPD, relative to wild-type MSC. We will test the ability of the engineered MSC/conditioned medium 1) in vitro, to characterize the ability of the cells/conditioned medium to improve endothelial cell signaling and function following exposure of human lung primary microvascular endothelial cells (HLMVEC) to cigarette smoke extract (CSE); and 2) in vivo, to determine whether this treatment can improve lung structure and function in a mouse model of smoking-induced COPD.

7/1/2014	Mao	Enhanced osteoblastic differentiation of iPSCs directed by phage assemblies with dual peptides displayed	Induced pluripotent stem cells (iPSCs) are considered as the best cell source for bone regeneration. However, they tend to form tumor-like structures if directly placed in human bodies. Thus they need to be first converted into osteoblasts (bone forming cells), a process called osteoblastic differentiation, before they can be used. Hence this project aims to discover small molecules that can induce the conversion of iPSCs only into osteoblasts. Bone morphometric protein 2 (BMP-2) is a large protein known to promote osteoblastic differentiation by allowing its two domains to bind to two respective cellsurface proteins (called receptor I and II). Our recent OCASCR-funded studies show that one short peptide, selected from a BMP-2 domain binding to receptor II, can induce osteoblastic differentiation of iPSCs. Since BMP-2 actually uses two separate domains to simultaneously bind to receptor I and II to trigger osteoblastic differentiation, we hypothesize that a combination of two BMP-2-derived peptides, selected from domains binding to receptor I and II, respectively, will more efficiently induce the osteoblastic differentiation of iPSCs. To prove this hypothesis, different combinations of such two peptides are co-presented on human-safe tiny fibers (called phage) by genetic means, which are further orderly or randomly assembled into substrates for supporting iPSCs growth. The osteoblastic differentiation is then verified by detecting the marker proteins unique for the formation of osteoblasts. This project will discover a combination of two novel peptide inducers that can most efficiently convert iPSCs into osteoblasts and understand whether its role is affected by substrate architectures.
7/1/2014	Pezza	Self-Renewal and Aurora Kinase-Dependent Chromosome Segregation in Spermatogonial Stem Cells	Spermatogenesis is the process in which spermatozoa are produced from spermatogonial stem cells (SSCs) and is required for sustained male fertility. Each SSC will continually divide to create more spermatogonial stem cells (self-renewal) and another cell type that will differentiate to eventually become mature spermatozoa. Adult human males produce approximately 100 million spermatozoa each day all originating from SSCs. In this process, accurate chromosome segregation is essential so that the appropriate chromosome number is maintained and passed on to subsequent generations. Indeed, errors in chromosome segregation can lead to abnormal chromosome number which may result in infertility and genome instability, the root cause of several testicular tumors. The Aurora kinase enzymes are important regulators of cell division and as such may have a central role in SSC self-renewal. Intriguingly, mammalian testes express two Aurora kinase isoforms, Aurora B and Aurora C. We and others have previously shown that these Aurora isoforms have both individual and overlapping functions in the late stages of spermatogenesis. However their role in SSCs and early stages of testis development has not yet been studied. In this proposal we will determine how and when Aurora B and Aurora C activities are required for SSCs proliferation. Additionally, we will reveal at the molecular level the role of each kinase in the accuracy of chromosome segregation during early spermatogenesis. The broader goal of our studies is to understand spermatogonial stem cell function, which has great potential for curative genetic treatments, and how they provide sustained male fertility.
7/1/2014	Pioszak	Engineering High-Potency “Superspondin” Adult Stem Cell Growth Factors	Adult stem cells hold enormous potential for regenerative medicine. In this application we propose research to study growth factors that stimulate the growth of adult stem cells of the intestine, stomach, colon, hair follicle, and skin. We will create modified versions of adult stem cell growth factors that will have increased ability to promote the growth of adult stem cells. The knowledge gained from these studies will guide the use of adult stem cell growth factors for regenerative medicine and provide novel therapeutics for intestinal disorders and cancer.
7/1/2014	Sansam	Enabling Technology-An Apparatus for Collecting Large Numbers of Embryos	A common aquarium fish called the zebrafish has become one of the most powerful experimental systems for understanding how the vertebrate embryo develops. We share many of the same genes with the zebrafish, hence what we learn by studying zebrafish development can tell us a lot about how a human embryo develops. Unlike humans, or even mice, zebrafish develop externally and can be very rapidly genetically manipulated. In fact, the zebrafish has been successfully used to identify drugs that promote the proliferation of stem cells in humans. We are using the zebrafish to study how the replication of the genome is controlled in stem cells. Our studies require daily collection of thousands of synchronously developing zebrafish embryos. Currently, this is a time consuming process that involves at least two technicians. We are requesting funds for a device that enables easy and rapid collection of zebrafish embryos at a defined developmental stage. Ultimately, our goal is to understand how stem cells can be manipulated for treatment of human diseases. This device would enable us to achieve that goal faster and at lower cost.

1/1/2014	Cohen	Role of caveolin-1 in limbal stem cell biology	The purpose of this project is to develop is to develop therapies to treat corneal blindness. The clear cornea is the outermost structure of the eye, which transmits light to the inside of the eye. The cells responsible for keeping the cornea clear are called limbal stem cells. These cells normally divide and proliferate to repopulate the cornea as well as heal the surface after a wound. Without proper wound healing, corneal blindness can result. We have found that a protein named caveolin-1 regulates the process of wound healing and that loss of this protein in a knockout mouse model leads to faster healing. Evidence suggests that caveolin-1 works by regulating stem cell proliferation. Our intent is to better understand this process and develop medications that can mimic the loss of caveolin-1 and accelerate wound healing.
1/1/2014	Olson	PDGF signaling in the adipocyte lineage and obesity	The incidence of obesity has increased dramatically in recent decades. This is a health concern because it is closely linked to cardiovascular and metabolic disease including type 2 diabetes. It has recently been shown that adipose tissue (fat tissue) contains adult stem cells that continually generate new adipocytes (fat cells) throughout life. Furthermore, these stem cells may have the ability to make different kinds of adipocytes: white adipocytes that are specialized for storing fat, and brown or beige adipocytes that are specialized for burning fat to generate heat. Some scientists believe that the ability to make many new adipocytes helps certain individuals store excess calories in a manner called "healthy obesity". By contrast, a shortage of new adipocytes contributes to unhealthy obesity and forces the existing adipocytes to exceed their healthy storage capacity, which worsens metabolic problems and contributes to diabetes. Additionally, many scientists believe obese patients would benefit from helping the body make more fat-burning (brown/beige) adipocytes instead of fat-storing (white) adipocytes. To realize these different therapeutic possibilities it is important to understand how adipose stem cells are regulated. However, these stem cells were only recently discovered and very little is known about them. The platelet-derived growth factor receptor-alpha (PDGFRa) has been instrumental in identifying adipose stem cells but it is not known if PDGF is needed for making new fat cells or if it regulates what kind of fat cells are made. The studies in my laboratory are designed to understand how PDGF controls the differentiation of stem cells into new adipocytes. We have a novel approach that utilizes cutting edge mouse genetic technology that we have developed in our laboratory. In short, we are creating mice with fluorescently labeled PDGFRa-mutant adipocyte stem cells in order to determine the requirement for PDGF in these cells. The benefits of this work lay in the future possibility of manipulating the PDGF pathway in adipose stem cells for therapeutic purposes.
1/1/2014	Rankin	Contributions of Cohesin and Condensin to Nuclear Reprogramming: an in vitro model for induced pluripotency	Stem cells have two fascinating properties: they can replicate themselves, and they have the capacity develop into many different cell types, a property referred to as pluripotency. Most cells in our bodies, such as those from skin or blood, have lost these properties, and are called “differentiated”. Something remarkable happens when the nucleus (in which all genes are packaged) from a differentiated cell is injected into an egg: it begins to acquire the properties of a stem cell nucleus. This is a process referred to as “reprogramming”. In some cases reprogrammed adult nuclei can even go on to make an entire organism, indicating that the transferred nucleus has become pluripotent! We are interested in the structural changes that occur when nuclei from differentiated cells are added to an egg. We have a system in which we can analyze these changes in a test tube, using extracts from frog eggs as a model. The experiments we propose will shed light on the nature of induced pluripotent stem cells, and may lead to new methods for turning differentiated cells into stem cells. Such adult stem cells would have enormous therapeutic potential, helping to treat a number of devastating human diseases.

1/1/2014	Sansam	The Role for DNA Replication Timing in Determining Cell Fate In Vivo	Researchers can now transform virtually any mature cell type taken from a patient's body into an induced pluripotent stem cell (iPS), which has the capacity to differentiate into any type of cell in the body. This iPS technology is emerging as a personalized therapeutic treatment option for a wide range of diseases. A current problem in iPS cell technology is the inefficiency by which cells can be reprogrammed. Many changes occur during the reprogramming of mature cells, so an important question is: which changes are essential and rate limiting? One distinct change in cells as they differentiate is in the order and timing that different portions of the genome undergo replication. Each cell type has a characteristic DNA replication timing profile, and the replication timing profiles of stem cells differ substantially from those of mature differentiated cells. The biological function of this replication timing program is unknown. A gene called Rif1 was recently shown to be required for normal DNA replication timing. We will test whether control over replication timing is essential for stem cell differentiation, by examining the effects of Rif1 knockout in cells as they transform from an early embryonic state to mature somatic cells in zebra fish embryos. The identification of genes and processes essential for stem cell differentiation and reprogramming is a crucial step in developing novel stem cell therapies.
1/1/2014	Wang	Understanding diabetes pathogenesis using patient-specific human iPS cells	One of the most important aspects of induced Pluripotent Stem Cell (iPSC) technology is modeling human diseases using patient-derived iPSCs. Our ultimate goal is to study the cause or etiology of Maturity Onset Diabetes of the Young (MODY) disease using MODY iPSCs and to develop new drugs to treat diabetes. MODY is a group of diabetic diseases which typically affect young people with a family history. Changes in a patient's DNA makeup have been found in MODY patients. However, how these genetic changes cause diabetes remains unclear, likely due to the lack of patient samples for research. Since their discovery, iPSCs have emerged as a way to generate disease-specific cell types. With this technology, skin cells from patients can be converted into a particular stem cell state by expressing four genes. The resulting iPSCs can be expanded in culture, and then be converted into cell types of interest. In this proposal, diseased iPSCs will be coaxed to become the pancreatic beta cells to study what went wrong in the diseased cells. The understanding of disease cause or pathology of MODY will further be used in large screens aimed to discover or test new drugs.
7/1/2013	Gaffney	Induced Pluripotent Stem Cells to Understand Influence of BLK Variants on Early B Cell Function	Systemic lupus erythematosus (SLE) is a complex human disease characterized by immune cell dysfunction. Recent research has identified a number of genes associated with the development of SLE. One of these genes, BLK, plays a large role in the development of B cells, important immune system cells that protect against infections and help maintain a balanced immune system. Mutations in the BLK gene have been found to be associated with the development of SLE. This project will use stem cells made from previously isolated adult SLE patient blood cells to create a variety of B cells. These cells will then be used to examine differences in cell development and function caused by mutations in the BLK gene.
7/1/2013	Gorbsky	Targeting Stem Cells in Cancer	All too commonly a patient undergoing cancer treatment shows a strong initial response with regression of the tumor followed by a disease-free period that can last years. Unfortunately, this remission is often followed by resurgence of therapy-resistant tumors. The cancer stem cell theory suggests that tumors reappear because current treatments are designed to kill rapidly dividing tumor cells that make up the bulk of the tumors but fail to target the small population of cancer stem cells. The cancer stem cells then give rise to resurgent tumors cells that are more aggressive and resistant to therapy. Researchers have been looking for ways to target cancer stem cells so that they can be killed along with the bulk tumor cells at the time of initial treatment. Dr. Jonathan Wren, our bioinformatics collaborator, has used computer analysis of publicly available genetic data from thousands of experiments to predict genes that are likely to be important for cell division of cancer stem cells. Using the technology of RNA interference, we will test the top 55 of these candidate genes to determine if they are specifically important for the division of breast cancer stem cells. The identification of essential cancer stem cell genes is a crucial step toward design of drugs that will target cancer stem cells in primary cancer therapy.
7/1/2013	Humphrey	Resetting the osteoarthritis epigenome using induced pluripotent stem cells	Osteoarthritis (OA) is a debilitating disease that affects one in three people in the U.S. over the age of 65, with a cost of lost productivity nearing $128 billion, yet we have yet to develop any therapy that will alter the progression of the basic biological processes that underlie the progressive cartilage destruction seen in OA. Recent research has highlighted the important role of epigenetics in the development and progression of OA. Epigenetics encompasses the various mechanisms that cells use to regulate in a semi-permanent fashion whether a particular gene is turned "on" or "off". Unfortunately, we have yet to develop ways to affect epigenetic marks at specific

			genes. Interestingly, however, previous studies have shown that converting a mature cell into a stem cell (specifically, induced pluripotent stem cell or iPS) requires significant alterations in the cell's epigenetic markers. In this study, obtain osteoarthritic cartilage cells from patients' joints when they undergo hip replacement surgery and attempt to "reset" their epigenetic state by converting them to iPS cells, then using certain growth factors to convert these iPS cells to normal cartilage. We will closely examine the epigenetic state of nearly all the genes in each cell during each of these three time points to confirm whether or not this process is effective. If successful, it may be possible in the future to convert arthritic cartilage cells back to "normal" cartilage cells, which would then be able to recreate a healthy joint without the need for extensive surgery or joint replacement.
7/1/2013	Pioszak	Structural Basis of R-spondin AdultStem Cell Growth Factor Signaling	Adult stem cells hold enormous potential for regenerative medicine. In this application, we propose research to study how growth factors stimulate the growth of adult stem cells of the intestine, stomach, colon, hair follicle, and skin. The proposed studies are designed to determine specifically how the growth factors bind to receptors on adult stem cells. The knowledge gained from these studies will guide the use of adult stem cell growth factors for regenerative medicine.
7/1/2013	Srinivasan	Molecular mechanisms of Foxc2action in lymphatic endothelial cell progenitors	The mammalian lymphatic vasculature is vital for the return of tissue fluids to the circulating blood. It also absorbs digested lipids from the intestine. Abnormal functioning of the lymphatic vasculature causes swelling of body parts, especially the limbs. This is known as lymphedema, a common disorder that results from either mutations in genes that regulate lymphatic vascular development or more often from surgical damage to the lymphatic vessels. It is estimated that 20-30% of breast cancer survivors develop lymphedema. Millions of women are thought to be suffering with lymphedema in the US alone. Currently, no cure is available for patients with lymphedema; therefore, only palliative treatments like massage are prescribed. Most of the tissues are thought to contain a few stem cells that function to repair mild to moderate tissue damage caused by aging. Efforts are ongoing to determine the identity of these adult stem cells and to enhance their ability to repair more severe tissue damage. We propose to identify the adult stem cells for the lymphatic vasculature, as this will be an important step in treating lymphedema.
1/1/2013	Barlic-Dicen	The role of the chemokine receptor CXCR2 in homing of endothelial progenitors to atheroregressing plaques	Atherosclerosis is a common disorder that leads to high morbidity and mortality. It occurs when cholesterol builds up in the arterial wall and forms plaques. As plaques grow they can break off and block blood flow in vessels, reducing supply of nutrients and oxygen, which causes tissue damage or death. This is a common cause of heart attack and stroke. Atherosclerosis is treated with cholesterol-lowering drugs called statins. Treatment with statins slows atherosclerosis from becoming worse, but can only cause partial plaque regression. Unfortunately, partially regressed plaques still pose a serious threat as they may break off. In order to avoid such complications in patients, we must learn how to treat plaques so that they will regress completely. We are investigating the role of endothelial progenitor cells for their ability to contribute to plaque regression. Most endothelial progenitors develop from bone marrow stem cells. Endothelial progenitor cells differentiate into endothelial cells that make up the blood vessel lining. We observed that lowering of blood cholesterol in mice resulted in partial regression of atherosclerosis. We also observed that if mice that already had atherosclerosis were given transfusions of endothelial progenitor cells, they regressed plaques better than animals that received no treatment. This indicates that endothelial progenitors improve plaque regression. However, how endothelial progenitors migrate to damaged arterial wall is unclear. This is important to know because it will improve our understanding of atherosclerosis regression and open the door for development of new anti-atherosclerosis therapies.
1/1/2013	Chen	The role of epsins in ISC expansion in Health and disease	Adult stem cell therapy has emerged as one of the most promising ways to conquer many intractable diseases. Remarkable progress has occurred in the past several years utilizing adult stem cells as novel therapies in regenerative medicine for disorders in blood systems. However, for intestinal diseases in which there is impaired regeneration or function of the small intestine or colon, such as in short bowel syndrome, inflammatory bowel disease, ischemic bowel, or following irradiation, stem cell-based therapies have lagged behind, partly because these therapies largely rely on the use of bone-marrow derived stem cells and mesenchymal stem cells. Additionally, for colon cancer in which colon cancer stem cells lead to a new population of colon tumor cells that are likely to be immune from most radio/chemo-therapies, stem cell-based interventions should undoubtedly bring breakthroughs in effective eradication of colon cancer. Although recent progress in the identification of adult intestinal stem cell (ISC) markers has fueled research that promotes using ISC to treat gastrointestinal disorders, identifying novel regulators that can increase ISC in cases where they are inadequate or diminish them where

			excessive, are necessary for a rapid translation of fundamental basic biological discoveries to therapeutic strategies. Our proposed study is to make groundbreaking discoveries concerning a new critical regulator in ISC maintenance and ultimately help us to control ISC expansion in diseased state. If successful, our work will potentially identify novel stem cell-based therapies for gastrointestinal disorders and provide new anti-colon cancer therapeutic targets.
1/1/2013	Cohen	Role of caveolin-1 in limbal stem cell biology	The cornea is the outermost clear covering of the eye responsible for transmitting light so that it can be detected by the internal structures of the eye. It is composed of living tissue that requires constant renewal and regeneration. A population of cells located at the edge of the clear cornea, known as limbal stem cells, is responsible for this task. These stem cells divide to normally repopulate the cornea and respond to stress, such as corneal trauma, to heal the corneal surface. When the cornea is injured, the limbal stem cells divide rapidly to fill in the area of damage. If this response is defective, blindness can result. The goal of this project is to test a novel strategy to manipulate stem cell function to develop more effective therapeutic strategies to modify the function of these stem cells. Our preliminary data suggest that potential corneal stem cells have high levels of a protein called caveolin-1. We have also found that mice that cannot express the caveolin-1 protein (knockout mice) heal corneal wounds faster than normal mice. We intend to better understand this process and use techniques that modify caveolin-1 protein levels to help heal corneal wounds in human patients by developing more effect stem cell transplantation.
1/1/2013	Liu	MicroRNA-mediated Differentiation of Induced Pluripotent Stem Cells into Alveolar Epithelial Type II cells: Mechanisms and Therapy for COPD	Chronic obstructive pulmonary disease (COPD) is a chronic lung disease. It is the fourth leading cause of death and affects over 16 million people in the USA. The major risk factor for COPD is cigarette smoking. There is no cure for COPD. The current treatment of COPD is palliative, with the goal of reducing symptoms and limiting recurrent exacerbations. The present proposal for adult stem cell therapy is intended to repair or replace damaged lung tissue. The success of this approach would therefore represent significant progress towards a cure for COPD.
1/1/2013	Lloyd	Mesenchymal stem cells and inflammatory signaling in COPD	Chronic obstructive pulmonary disease (COPD) is a major public health issue in Oklahoma, which had the highest age-adjusted death rate from COPD for all 50 US states in 2005. Certain growth factors have been implicated in the development of COPD. The goals of this study are to 1) gain new mechanistic insights into the role of growth factor signaling in COPD and 2) determine whether beneficial effects of mesenchymal stem cells are related to inhibition of abnormal growth factor signaling. These studies may also be relevant to other diseases in which growth factor signaling is abnormal, including sickle cell anemia and cancer.
1/1/2013	Lupu	Role of Androgen-dependent TFPI Regulating Protein (ADTRP) in mesenchymal stem cell differentiation	Our newly discovered protein ADTRP is important for the transformation of bone marrow- derived adult stem cells (ASC) into fat or bone. The male hormone testosterone heightens the formation of muscle and bones in young adults, reduces fat, and maintains healthy blood vessels through factors that oppose unwanted blood clots. We found that testosterone and ADTRP are directly correlated. Testosterone's decline with advancing age accelerates obesity, functional deficiencies, and possibly cardiovascular disease (CVD). ASC self-renew and transform into fat, bone or muscle. Our work could reveal how to make ASC switch between these cell types, as well as switch between the "bad" white fat that stores calories and the "good" brown fat that releases energy. We modified ASC to have higher or lower ADTRP and observed that reducing ADTRP heightened white fat formation, whereas increased ADTRP skewed fat accumulation toward brown fat. Brown fat is mainly in babies to maintain the body's core temperature, but we lose it with aging. ASC made into brown fat through the action of ADTRP could help people lose weight. Testosterone may help this process, especially for the elderly. Since variations in the DNA sequence (SNPs) in ADTRP correlate with increased severity of CVD, ADTRP may offer vascular protection. We expect to observe more severe hardening of the vessel wall (atherosclerosis) in mice where the gene responsible for ADTRP was removed. Heightening of ADTRP in vascular multipotent cells could enlist them to reduce plaque (fat deposits) in the blood vessels, which would prevent plaques from coming apart and provoking heart attack and stroke.
1/1/2013	Mao	Genetically displaying peptides to direct osteogenic	Induced pluripotent stem cells (iPSCs) are promising cell sources for tissue regeneration because they can overcome immune rejection and bypass the ethical issue of embryonic stem cells. In bone regeneration, iPSCs should be specifically transformed into bone forming cells (called osteoblasts), a process called osteogenic

		differentiation of iPSCs on nanopatterns	differentiation. However, there is a great need for molecules that can induce their differentiation specifically into one type of cells such as osteoblasts. Our recent studies funded by OCASCR show that a peptide derived from bone morphometric protein-2 (BMP-2), a natural protein found in bone, can induce the osteogenic differentiation of iPSCs. This exciting discovery inspires us to propose the further systematic study of the osteogenic differentiation of iPSCs on a biomaterial, which single- or double-displays different molecular domains (called peptides) of BMP-2. Such study will lead to the discovery of a single peptide or a combination of two peptides that can induce the osteogenic differentiation of iPSCs most efficiently. Towards this end, a non-toxic bio-nanofiber called phage is first genetically engineered to surface-display one or two peptides selected from BMP-2 and then self-assembled into biomaterial films with different peptides but constant architecture. iPSCs will then be cultured on the films and characterized to verify their osteogenic differentiation. Although the native BMP-2 can induce osteogenic differentiation in bone, it is very expensive and exhibits immune-related side effects. Therefore, this project will identify BMP-2-derived differentiation-inducing peptides to advance the field of tissue regeneration and develop a phage-based technology for studying stem cell biology.
1/1/2013	Sun	Asb2 in normal and cancer stem cell biology	Hematopoietic stem cells (HSC) are responsible for replenishing blood cells throughout life. For example, the life span of red blood cells is 90 days; they needed to be constantly replaced by new ones, which are made from HSC through well-controlled differentiation programs. The number of HSC is limited in the body. Although they can normally renew themselves, this capacity is limited. A better understanding of the control of HSC renewal could lead to practical applications that will benefit bone marrow transplantation for patients with various blood disorders and leukemia. When blood formation malfunctions and blood cell growth becomes out of control, cancer develops in the blood, which is called leukemia. The majority of cancerous blood cells are derived from a small group of cancer stem cells, which serve as the seeds for cancer cells. Although drugs are available to kill the cancer cells, the cancer stem cells are not sensitive to the same treatment and therefore the seeds remain. Both HSC and cancer stem cells use similar strategies to maintain themselves, which makes cancer treatment difficult. The challenge now is to find the differences between these two types of stem cells so that we can kill the latter without hurting the former. The proposed study is aimed at understanding the regulation of normal and cancer stem cell growth by studying the function of one of the central regulators. If this regulator is found to impart differential effects, it could become a therapeutic target.
1/1/2013	Tsiokas	Calcium signaling in bone marrow-derived stem cells	Healthy bone maintains a balance of bone formation mediated by osteoblasts and bone resorption mediated by osteoclasts. Many disease states, including chronic periodontitis, osteoporosis, rheumatoid arthritis, Paget's disease, and cancer metastases develop when osteoclasts are excessively recruited or inappropriately activated. Osteoclasts are constantly made throughout life from hematopoietic stem cells residing in the bone marrow. It has been long recognized that ionized Ca2+ has an essential role in the formation of osteoclasts. However, the exact molecules and mechanisms by which Ca2+ regulates osteoclastogenesis are largely unknown. We have found that the Transient Receptor Potential Ca2+ channel, TRPC1, enhances osteoclastogenesis, whereas its inhibitor, called I-mfa, has an opposite effect. Genetically engineered mice lacking I-mfa show a severe form of osteoporosis, which is corrected in mice lacking both genes. Therefore, we propose that TRPC1 and I-mfa are essential for osteoclast formation by regulating the levels of ionized Ca2+ into the cell. This hypothesis will be tested by asking whether and how TRPC1 and I-mfa affect an early stage of osteoclast formation from hematopoietic stem cells. Our studies will lead to further understanding of critical pathways in the regulation of osteoclast development and function, which is needed to identify and develop new therapeutic interventions to control osteoclastogenesis and prevent bone loss.
1/1/2013	Zhang	The Role of Breast Cancer Stem Cell in Cancer Invasion and Metastasis	Breast cancer (BCa) is the most common cancer and the leading cause of death due to cancer among women in USA. The major death directly caused by BCa results from the aggressive BCa that metastasizes to bone, lung, brain, or other organs to kill patients. Thus, the prevention, diagnosis, and treatment of the aggressive or metastatic BCa become pivotal in the battle against BCa. Unfortunately, how BCa becomes aggressive or metastatic is still unclear. Recently, cancer stem cells are proposed to play an important role in cancer initiation. Whether or not cancer stem cells facilitate or even determine cancer invasion and metastasis remains largely unknown. The major goal of this project is to determine whether or not BCa stem cells cause BCa to 1) infiltrate into surrounding tissues and 2) disseminate to distal organs. If yes, we will further determine how BCa stem cells drive BCa metastasis. The results from this study will significantly enhance our understanding of BCa metastasis

			as well as the function of cancer stem cell. From clinical point of view, understanding of the roles of BCa stem cells in BCa invasion and metastasis will lead to the development of therapeutics specifically blocking BCa metastasis. Because BCa is an adult disease, BCa stem cells obviously fall into the category of adult stem cells.
7/1/2012	Carr	HSV-1 Infection and Neuronal Stem Cell Differentiation	Herpes simplex virus type 1 (HSV-1) is a common human viral pathogen and is the leading cause of frank sporadic encephalitis, a rare but often devastating illness that even with effective treatment can leave the patient neurologically debilitated experiencing memory loss and motor dysfunction. Unfortunately, the patient population most at risk includes the very young and elderly citizens. Presently, it is not understood why patients that survive a bout of HSV-1 encephalitis often experience lifelong neurological dysfunction. Using a mouse model to investigate HSV-1 encephalitis, we have discovered a significant tropism of the virus to one of two sites in the brain, the ependyma, where neuronal stem cells (NSC) reside. Using a NSC line, we have found HSV-1 successfully infects the cells and reduces differentiation favoring neurons to one favoring oligodendrocytes. We hypothesize the neurological problems experienced by HSV-1 encephalitis survivors may be the result of a loss of NSC to differentiate into neurons in response to those neurons lost as a result of necrosis/apoptosis during the encephalitic incident. We propose to further investigate this observation using the NSC line in vitro along with an organotypic brain slice culture. We anticipate the support of this project will identify key factors involved in the aberrant NSC behavior in response to HSV-1 which may ultimately lead to a treatment for patients that survive HSV encephalitis as well as other debilitating diseases of the central nervous system that compromise NSC differentiation.
7/1/2012	Olson	Mechanisms of Wound Repair by PDGF and Endogenous mesenchymal Stem Cells	Our bodies have the capacity to repair themselves through an intricate process that closes the wound and returns the damaged tissue to a functional state. This works remarkably well when we are young, but not as well when we age. Non-healing chronic wounds commonly occur in the elderly and those who have poor circulation due to diabetes or immobility. There is a tremendous need for new technology to solve the medical problems of non-healing wounds, and this can only come through a better understanding of the repair process. Injured or stressed tissues produce a small protein signal called platelet-derived growth factor (PDGF). Some cells have specific PDGF-receptors located on the cell surface that allow them to sense PDGF in the wound environment. PDGF stimulates wound repair, but too much PDGF causes scar tissue. Therefore, our bodies must maintain a careful balance for proper healing. Some adult stem cells, called mesenchymal stem cells (MSCs), have PDGF-receptors. It is not known why MSCs have PDGF-receptors or if they are important in the overall wound-repair process. We hypothesize that MSCs may hold the key to optimal tissue repair via their response to PDGF in the wound environment. The studies in my laboratory are designed to understand how PDGF works in wound repair and how MSCs are involved. We study genetically engineered mice with altered PDGF receptors in their MSCs to understand how they are involved in wound repair. By understanding the function of MSCs we hope to improve therapies for chronic wounds.
7/1/2012	Pioszak	Recognition of R-sponsin Adult Stem Cell Growth factors by LGR Receptors	Adult stem cells hold enormous potential for regenerative medicine. If we are to realize their full therapeutic potential it is essential that we develop a thorough understanding of how adult stem cells grow in their natural environment inside the body and in culture in the laboratory. We are studying growth factors known as R-spondins, which potently stimulate the growth of adult stem cells of the intestine, stomach, colon, hair follicle, and skin. R-spondins hold promise for their use in tissue regeneration. The studies in this proposal are designed to determine how R-spondins bind to receptors on the surface of adult stem cells. This is important because receptor binding is required for R-spondins to stimulate adult stem cell growth. The knowledge gained from these studies will guide the use of R-spondins for regenerative medicine purposes.

7/1/2012	Wang	Generation of TALEN-based knock-in fluorescent reporter human iPS cells for dissecting β-cell differentiation	Our long-term goal is to develop a cell-based therapy to replenish insulin-producing β-cells for the purpose of treating type 1 diabetes (T1D), in which >90% β-cells are destroyed. The remarkable developmental and differentiation potential of induced pluripotent stem cells (iPSCs) makes them attractive candidates for cell-based therapies. However, the efficiency of β-cell differentiation from iPSCs with current protocols is low, and the resulting insulin-producing cells exhibit minimal responses to glucose stimulation. It is, therefore, necessary to understand the complex signaling that controls this differentiation and precisely direct their differentiation in culture, before the full potential of iPSCs can be realized. Using novel TALEN technology in tandem with cell biological and gene expression profiling approaches, the planned research will drastically improve our understanding of molecular and cellular programs underlying human β-cell differentiation, maturation and function. With our experience in iPSC derivation and β-cell differentiation, we are well-positioned to achieve all of our aims. Successful completion of the proposed studies will provide insights into how to efficiently derive functional human β-cells and accelerate efforts to create stem cell based therapies for T1D.
7/1/2012	Webb	Mechanisms by which ARID3a Affects Human Pluripotency Gene Expression	In the past few years it has become possible to use adult tissues to “reprogram” cells into stem cell-like cells that can then be used to make a wide variety of other cell types. These advances have the potential to be used for cell or tissue replacement therapies and to help make new discoveries about the underlying causes of some kinds of diseases. We discovered a new mechanism for “reprogramming” human cells that may avoid some of the problems associated with the techniques other people use. One such problem is that reprogrammed cells may retain information that causes them to “remember” what kind of cell they came from. This epigenetic information can interfere with the ability of cells to be used to replace other kinds of tissues. The purpose of the proposed studies is to discover whether our method for reprogramming cells avoids this problem and to develop a better understanding of exactly how our method differs from those used by other people. Our studies will provide important new information about how reprogramming changes cells so that we can improve the usefulness of these cells for regenerative medicine.
1/1/2012	Alberola	Development of an in vitro model of LPS-induced alterations in HSC function.	Our immune systems become less effective in old age, and there is new evidence to suggest this can result from a history of low-grade infections. It is difficult to analyze how these low grade infections affect the stem cells that give rise to our immune system in whole animals. This project will develop methods to reproduce this phenomenon in cell culture, so we can study it better. More study could reveal how to block or even reverse these consequences of aging.
1/1/2012	Hinsdale	Adult Stem cell proteoglycans and emphysema	Chronic lower respiratory disease including emphysema is the second leading cause of death in Oklahoma and no specific treatment is available. The major risk factor for disease is cigarette smoking. Adult stem cells are known to be involved in the attempts by the body to heal the damaged lung. Subsequently, there is an increasing interest in adult stem cell-based therapies. Special proteins called proteoglycans influence the behavior of many cell types including adult stem cells. Proteoglycans are decreased in emphysema and likely influence the development and severity of the disease. The current project will determine how proteoglycans affect the ability of adult stem cells to participate in recovery from emphysema with specific focus on endothelium. Furthermore, strategies are proposed to develop adult stem cell therapies manipulating proteoglycan levels to ameliorate disease development and severity. The completion of this project will not only advance our understanding of the biochemical mechanisms in the behavior of adult stem cells, but also lead to potentially clinical applications of adult stem cell therapy to human lung disease.
1/1/2012	Liu	Cell-based Therapy of COPD using induced pluripotent stem cell-derived alveolar Epithelial Type II cells	Chronic obstructive pulmonary disease (COPD) is a chronic lung disease. It is the fourth leading cause of death and affects over 16 million people in the USA. The major risk factor for COPD is cigarette smoking. There is no cure for COPD. The current treatment of COPD is palliative, with the goal of reducing symptoms and limiting recurrent exacerbations. The present proposal for adult stem cell therapy is intended to repair or replace damaged lung tissue. The success of this approach would therefore represent significant progress towards a cure for COPD.

1/1/2012	Lloyd	Mesenchymal stem cell therapy to support maintenance and repair of lung vasculature in experimental COPD	Emphysema, a form of chronic obstructive pulmonary disease (COPD), is a severe chronic lung disease for which there is currently no effective treatment. In the lung, oxygen exchange occurs in the alveoli. Capillaries are located in the walls between alveoli, allowing oxygen to diffuse from the alveoli into the blood. Normal alveolar structure is lost in COPD, and many studies have suggested that loss of alveoli is linked with loss of lung capillaries. It has also been shown that disturbances in the expression pattern of a key growth factor family, the vascular endothelial growth factor (VEGF) family, contribute to the development of COPD. Mesenchymal stem cells (MSC) are a type of adult stem cell that has been shown to support vascular growth and aintenance, in part by acting on the VEGF pathway. Thus, we hypothesize that MSC might be useful for the treatment of COPD. In this study we propose to alter VEGF family gene expression in MSC and then test whether they can be used to treat COPD. We will examine lung structure, lung function, and lung vascularity to determine if the stem cell treatment is effective. Results of this study will suggest ways in which stem cells might be used as a treatment for COPD and will show whether the effect of stem cell therapy can be enhanced by normalizing VEGF family signaling. Increased maintenance/repair of lung capillaries may enhance alveolar repair and improve lung function. Patients with other chronic lung diseases may also benefit from this research.
1/1/2012	Lupu	Role of the novel lipid-raft organizer, ADTRP/C6orf105 on the differentiation of mesenchymal stem cells	We discovered a novel protein ADTRP, which is produced by the adult stem cells (ASC) in the bone marrow that give rise to muscle, bone or fat. ADTRP is increased by the male hormone testosterone, which also heightens the formation of muscle and bones in young adults. Low testosterone relates to obesity, and functional deficiencies in elderly men. If increased ADTRP can create platforms on ASC for testosterone to gather, it will help make muscle and/or bone rather than fat and fight against obesity. Our work may reveal how to switch the most common “bad” white fat that stores calories into “good” brown fat that releases energy. Brown fat is mainly in babies to maintain the body’s core temperature, but we lose it with aging. Therapy with ASC engineered to become brown fat through the action of ADTRP and testosterone could help people lose weight. Lack of ADTRP is seen in the congenital (present at birth) diseases craniosynostosis (joints on a baby's head close earlier than normal, which weakens the brain function) and “cleft lip and palate” (the two skull plates that form the roof of the mouth are not completely joined), which occurs in 1/700 live births worldwide. We think that ACS modified to have more ADTRP could prevent these diseases, and also fight against fat deposits (plaque) in the blood vessels, by producing muscle or fiber to enforce the weakened vessels and prevent the plaque to come apart, events that lead to heart attacks and frequently to death.
1/1/2012	Mao	Peptide-stimulated osteogenic differentiation of induced pluripotent stem cells	Reprogramming somatic cells to possess pluripotency similar to embryonic stem cells (ESCs) is promising development in the field of cell therapy. These cells, termed induced pluripotent stem cells (iPSCs), have the potential to differentiate into a variety of cell lines and circumvent the ethical dilemma of using ESCs. However, directing the cells down a specific differentiation pathway so that they can be used in clinical applications remains a challenge. In this work, we selected four active sequences derived from extracellular matrix proteins that are known to promote the differentiation of adult stem cells and examined their effect on the differentiation of iPSCs toward bone forming cells called osteoblasts. Using genetic engineering techniques, we are able to display these selected active peptide sequences on the surface of bacteriophage, a naturally-occurring biological nanofiber. Based on a technique we developed in previous work, we will assemble these modified nanofibers into a highly ordered film and allow the iPSCs to proliferate and differentiate on it. By examining the morphology of the iPSCs and the proteins that they produce, we will be able to determine how certain selected active sequences effect the differentiation of iPSCs. We hypothesize that at least one of the active peptide sequences displayed on the bacteriophage will cause the iPSCs to differentiate toward osteoblasts. This project will lay foundation for our further work on using iPSCs in bone regeneration. In the future, we will use a bacteriophage scaffold to support iPSCs and evaluate its application in bone regeneration in animal model.

1/1/2012	Naash	Enhancing Retinal Progenitor Cell integration in the Model of Retinitis Pigmentosa	Retinitis pigmentosa is a group of genetic eye disease in which dim light vision, mediated by rod photoreceptor cells, is lost first and bright light vision, mediated by cone photoreceptor cells, is lost later. The cause for the secondary degeneration of cones is unknown but previous results suggest that loss of integrity of the retinal outer limiting membrane may contribute. Interestingly, it has been shown that transplanted retinal stem cells may integrate better in cases where the outer limiting membrane has been interrupted. In this application, we propose to test the hypothesis that delivery of isolated retinal stem cells at a time after which outer limiting membrane defects are apparent but before secondary cone degeneration has begun will enhance cell integration and uptake and may delay the degeneration and loss of vision associated with retinitis pigmentosa.
7/1/2011	Barlic-Dicen	Roles of the chemokine receptor CXCR4 in adipogenic progenitor cell mediated hyperplasia	Obesity is rapidly escalating in the Western hemisphere. This increase is common across age and gender with a particularly alarming rate of increase in children. It is becoming the most serious public health problem of the 21st century. Obesity develops when excess body fat accumulates to unhealthy levels, reducing life expectancy and increasing the incidence of diseases such as heart disease and diabetes. Development of obesity is more complex than simply overeating. Understanding how it develops will be critical to improve lives and longevity, and to reduce a staggering burden on the healthcare system. Two major ways that fat tissues expand are the enlargement of fat cells (adipocytes) or an increase in their numbers. Mechanisms that increase adipocyte size are well-studied. In contrast, mechanisms promoting increased adipocyte numbers are not well understood. It is known that numbers of fat cells in fatty tissues increase when cells that are not adipocytes, but can differentiate into them, undergo maturation. These immature preadipocytes can reside within fat tissue or migrate into fat from outside sources such as bone marrow. We found that a specific cell-surface receptor CXCR4 is a major regulator of obesity in mice. Our data lead us to suspect that it may control body weight by increasing the number of fat cells. Thus, we will study whether CXCR4 affects maturation of pre-adipocytes or their migration from bone marrow. This is important to know because it will improve our understanding of obesity and may allow the development of new antiobesity therapies.
7/1/2011	Tsiokas	Calcium signaling in mesenchymal stem cells	The adult bone marrow contains a pool of multipotent stem cells that can give rise to osteoblasts (bone cells), adipocytes (fat cells), chondrocytes (cartilage cells), cells forming the tendons, skin cells, and muscle cells. These cells are called mesenchymal stem cells or multipotent stromal cell (MSCs). Understanding the cellular mechanisms by which MSCs follow these distinct cell fates is fundamental in combating diseases associated with skeletal and muscular defects, obesity, and diabetes. We have discovered a new role of Ca2+ ions in affecting the differentiation process of progenitor MSCs to mature osteoblasts. Specifically, we found that the Ca2+-permeable TRPC1 ion channel is essential for the maintenance of the progenitor pool of these cells by promoting self-renewal and proliferation. In the absence of TRPC1, MSCs exit the cell cycle and differentiate prematurely. Consistently, mice lacking the trpc1 gene have increased bone density. We propose that the mechanism by which TRPC1 maintains MSCs in the proliferating stage is by allowing ionized Ca2+ into the cell in response to growth factors. Incoming Ca2+ initiates a process that is required for the continuous proliferation of the MSCs. In this proposal, we will delineate the process by which TRPC1-mediated Ca2+ entry maintains a normal level of proliferation of MSCs. Successful completion of the study will set the stage for new approaches to combat osteoporosis and other diseases associated with bone loss.
7/1/2011	Wang	Small molecules that replace OCT4 during induction of human iPS cells	Pluripotent stem cells such as embryonic stem (ES) cells have a remarkable potential to develop into virtually any cell type of the body, making them a powerful tool for the study or direct treatment of human diseases. Recent demonstration that induced pluripotent stem (iPS) cells can be made from adult cells offers unprecedented opportunities for basic biology research, cell transplantation therapy, disease modeling, and drug discovery. Like ES cells, iPS cells can be turned into virtually any cell type in the body, but unlike ES cells, iPS cells do not involve the destruction of embryos or oocytes, thus circumventing ethical issues surrounding ES cells. iPS cells can also be made from the same patient, thus circumventing immune rejection related to transplantation from other donors. However, significant hurdles need to be overcome before the full clinical potential of iPS cells is realized. Currently, iPS cells are generated by forced expression of four molecular factors using viruses, which will be integrated into the DNAs of a patient's cells. This may lead to mutations and altered properties of iPS cells, as well as tumorogenesis if transplanted back into the patient. We propose to identify small molecule chemicals that can replace the virus-based delivery to generate virus integration-free iPS cells by screening large number of chemicals. Application of these small molecules will not only help overcome issues associated with viral

			integration but also has the potential to transform personalized cell-replacement therapies and to accelerate drug discovery based on iPS cell-derived disease models.
7/1/2011	Webb	ARID3a and Induction of Pluripotency in Human Cells	It has recently become possible to use adult tissues to “reprogram” cells into stem cell like cells which can then be used to make a wide variety of other types of cells. These advances have great potential for cell or tissue replacement therapies. We recently discovered a new mechanism for converting cells to a more developmentally plastic state and have made considerable progress in experiments using mouse cells in this way. Our technique increases the efficiency of “reprogramming” considerably in these cells. However, reprogramming human cells often requires slightly different techniques than those used with mouse cells. The proposed studies will define conditions that allow reprogramming of adult human somatic cells into stem cell-like cells. In addition, they will attempt to characterize the mechanisms by which our techniques allow reprogramming to occur. These studies will result in useful information that will accelerate development of more effective tissue replacement therapies.
1/1/2011	Houchen	Role of Adult Stem Cells in Pancreatic Regeneration and Diabetes Treatment	23.6 million people in the US, and nearly 200 million worldwide have diabetes causing high blood glucose levels. The high glucose levels are due to impaired production of the hormone insulin in beta-cells of the pancreas. High blood glucose levels damage nerves and blood vessels, leading to complications such as heart disease, stroke, blindness, kidney disease, and gum infections. We have done some studies with mice that may lead to promising work related to diabetes. The goals of this project are to identify if pancreatic stems cells can be converted into insulin producing cells and to determine their role in replacing damaged pancreatic cells. A more complete understanding of the restorative process of pancreatic beta-cells will pave the way for the development of medicine based treatments for diabetes.
1/1/2011	Naash	Retinal Stem Cells	The ultimate goal of this research is to use retinal progenitors that have stem cell properties to replace cells in the retina that have been damaged as a result of eye diseases such as age-related macular degeneration (AMD) or retinitis pigmentosa (RP). Unlike normal retinal cells, retinal progenitors possess the ability to grow, multiply, and change into different retinal cell types in the retina. Most importantly, they can change into the cells that are responsible for sending visual signals to the brain. Although some therapies have shown great promise in stopping the progression of retinal disease, these approaches do not promote creating new cells to replace the damaged cells. Our approach offers the greatest possibility for restoring vision in these cases by replacing the damaged or killed cells with retinal progenitor cells. The transplanted cells will differentiate into the right kind of cell type that will then restore sight. We will do this research by taking cells from genetically modified mice and transplant them into the diseased eyes of mice. This will allow us to determine how well the new cells can help improve the retina and vision.
1/1/2011	Sun	Role of Id1 in bone marrow niche and mesenchymal stem cell differentiation	Mesenchymal stem cells (MSCs) can be found in a variety of adult tissues, for example, bone marrow and fat. These cells can to be coaxed to turn into many types of cells. Therefore, it may be possible to use MSCs taken from the fat tissues which are discarded after liposuction to repair damaged heart muscles and some back problems. In this study, we will learn about the properties of MSCs and how to guide them to become a desired cell type. In addition, we will study how MSCs in the bone marrow influence blood stem cells which are responsible for the ongoing replacement of blood. When the body has an infection, particularly chronic infection, blood cell formation is impaired. We will determine if this is due to the damage to the blood stem cells themselves or to the environment created by the MSCs. The knowledge we gain will help design interventions that will protect blood stem cells to ensure proper blood supply.

1/1/2011	Xia	Glycoengineering of endothelial progenitor cells for therapeutic neovascularization in ischemic stroke	Stroke is currently the third leading cause of death in the United States, and a leading cause of serious, long-term adult disability. Oklahoma ranks 5th in stroke death rates in the US. The American Stroke Association estimates that $73.7 billion will be spent on stroke-related health and disability costs in 2010. Stroke is caused by a build-up of fatty deposits on blood vessel walls. This condition damages the cells lining the blood vessels and can lead to clots that block blood flow to the brain; this is the most common form of stroke. It has recently been found that there is a potential to transplant stem cells to repair the damaged cells in the blood vessels. The stem cells attach to specific, matching tissue cells and can replace the damaged vessels. However, in this treatment, only a small number of the stem cells will attach to the damaged cells. We have found a particular method that will increase the number of cells that attach which therefore will increase the repair of the damaged vessels. The ultimate goal of this project would be to develop a treatment for stroke, reducing disability, mortality, and healthcare costs.
7/1/10	Hinsdale	Adult Stem cell proteoglycans and emphysema	Chronic lower respiratory disease including emphysema is the second leading cause of death in Oklahoma and no specific treatment is available. The major risk factor for disease is cigarette smoking. Since adult stem cells are known to be involved in the attempts by the body to heal the damaged lung, there is an increasing interest in adult stem cell-based therapies. A unique group of proteins called proteoglycans influences the behavior of many cell types including adult stem cells. As a result, the decreased proteoglycans in patients' lungs likely influences the development of disease. The current project will determine how proteoglycans affect the ability of adult stem cells to participate in the body's attempts at recovery from emphysema. The completion of this project will not only advance our understanding of the biochemical mechanisms important in the behavior of adult stem cells, but may also lead to clinical applications of adult stem cell therapy to human lung disease.
7/1/10	Liu	Reprogramming of Adult Lung Cells for Cell-based Therapy	Chronic obstructive pulmonary disease (COPD) is a chronic lung disease. It is the fourth leading cause of death and affects over 16 million people in the USA. The major risk factor for COPD is cigarette smoking. There is an increasing interest in adult stem cell-based therapy, which eliminates the social and ethical concern in the application of embryonic stem cells. MicroRNAs are tiny molecules in cells that essentially control every biological process in the body. The current project will utilize microRNAs to convert adult lung cells to stem cells and then test whether these cells can be used to cure COPD. The completion of this project will not only advance our understanding of molecular mechanisms in the generation of adult stem cells, but could also lead to clinical application of adult stem cells in human lung diseases.
7/1/10	Lloyd	Endothelial progenitor cell survival and function in emphysema: role of VEGFA/ PLGF signaling	Emphysema is a severe chronic lung disease for which there is currently no effective therapy. For oxygen to travel effectively from the lungs into the blood, lung alveoli have to be matched equally with lung capillaries. Considerable evidence suggests that if capillaries are damaged, the alveoli they are located near become damaged also. This prevents the normal transport of oxygen from the lung into the bloodstream, and thus not enough oxygen goes to the rest of the body. Endothelial progenitor cells (EPC) are a type of adult stem cell which can repair damaged capillaries. However, this repair does not seem to occur in emphysema. We will study 1) how the vascular endothelial growth factor (VEGF) family affects the survival of EPC and 2) whether manipulating VEGF genes can enhance EPC survival and promote lung self-repair in emphysema. Results of this work may have implications for drug treatments that could improve the symptoms of emphysema. Patients with other chronic lung diseases may also benefit from this research.
7/1/10	Tsiokas	Calcium signaling in mesenchymal stem cells	The adult bone marrow contains multipotent stem cells that can become osteoblasts (bone cells),adipocytes (fat cells), chondrocytes (cartilage cells), cells forming the tendons, skin cells, and muscle cells. These cells are called mesenchymal stem cells or multipotent stromal cells (MSCs). Understanding how MSCs become the different types of cells is fundamental in fighting diseases associated with skeletal and muscle defects, obesity and diabetes. We have discovered, through our studies with mice, that it may be a new way to increase bone strength. Successful completion of the study will set the stage for new approaches to combat osteoporosis and other diseases associated with bone loss.

7/1/10	Webb	Generating Adult Stem Cells Using the Transcription Factor Bright/ARID3a	Recent advances in stem cell research allow adult cells from skin or blood to be changed or “reprogrammed” to become stem-like cells. These adult-derived stem cells have the potential to be purposefully directed to become other types of mature cells useful for cell or tissue replacement therapies. However, the current methods used to produce such cells are not clinically useful because they are inefficient and the stem cells that they produce are prone to form tumors. We have discovered a new method to produce reprogrammed cells which shows a high potential for overcoming these problems. The proposed studies will allow us to develop this method with the goal of efficiently generating better stem cells. This will increase the pace of stem cell research and accelerate development of more effective tissue replacement therapies.