

**FY11 Oklahoma Health Research Review**  
**Summaries of Proposals Recommended for Funding**  
**May 17, 2011**

Principal Investigator: <b>Roger Harrison</b>	Project Title: <b>Enzyme Prodrug Therapy to Treat Metastatic Breast Cancer</b>
Project Number: <b>HR11-210</b>	Organization: <b>University of Oklahoma</b>
Rank: <b>1</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The purpose of this project is to develop an effective enzyme prodrug therapy for metastatic breast cancer by evaluating three different enzymes—L-methioninase, cytosine deaminase, and purine nucleoside phosphorylase—in which the enzyme is targeted by the protein annexin V to the breast tumor vasculature, using a prodrug appropriate for the specific enzyme. Metastatic breast cancer is usually not curable. The median survival of women with metastatic breast cancer is approximately two years after documentation of metastasis, and the treatment for most patients is considered palliative in nature. Therefore, an effective therapy for this disease would have a tremendous impact. The results of this project could possibly be commercialized by a biotechnology or pharmaceutical company in Oklahoma or elsewhere, leading to economic development and to licensing royalties to the university.
Research Area	<b>Biomedical Engineering</b>

Principal Investigator: <b>Courtney Griffin</b>	Project Title: <b>Epigenetic Regulation of uPA During Vascular Development</b>
Project Number: <b>HR11-013</b>	Organization: <b>Oklahoma Medical Research Foundation</b>
Rank: <b>2</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Vascular leakage and rupture cause numerous pathologies in humans, including cardiovascular collapse and aortic aneurysms. This research team has generated a novel mutation in the chromatin-remodeling enzyme Chd4 that results in vascular rupture and massive hemorrhage during embryonic development. Preliminary data indicate that this phenotype is caused by overproduction of the urokinase-type plasminogen activator (uPA), a serine protease that triggers a proteolysis cascade resulting in extracellular matrix degradation. Since extracellular matrix proteases have been implicated in heart failure, aneurysms, and tumor angiogenesis, a thorough understanding of their regulation will impact a number of vascular-related disorders. These studies will establish whether CHD4 might serve as a novel therapeutic target for cardiovascular diseases stemming from compromised vascular integrity.
Research Area	<b>Cell/Molecular Biology</b>

Principal Investigator: <b>John Masly</b>	Project Title: <b>The Genetics of Morphological Differences in Drosophila</b>
Project Number: <b>HR11-031</b>	Organization: <b>University of Oklahoma</b>
Rank: <b>3</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The study of the genetic basis of species-specific differences in the size and shape of morphological traits in Drosophila is widely applicable to the study of tissue growth and morphology in other species, including humans and their primate relatives. In particular, variation among genes in the insulin signaling pathway, a well-known biological pathway that controls organ and tissue size and shape, appears important for establishing morphological differences between species. Defects in many of these genes have been implicated in some forms of diabetes and cancer. The proposed work is thus relevant to public health because the information learned from this study can be applied to understanding how change in genes important for regulating cell and tissue growth translate into human diseases.
Research Area	<b>Evolutionary Genetics</b>

Principal Investigator: <b>Augen Pioszak</b>	Project Title: <b>Modulation of Class B GPCR Hormone-binding by RAMPs</b>
Project Number: <b>HR11-080</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>4</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The calcitonin receptor-like receptor (CLR) is a cell surface G protein-coupled receptor that mediates the potent vasodilatory actions of the peptide hormones calcitonin gene-related peptide (CGRP) and adrenomedullin (AM). The selective binding of CGRP or AM to the CLR is determined by three receptor activity modifying proteins (RAMPs). Association of CLR with RAMP1 gives rise to CGRP receptors, whereas AM receptors arise from RAMP2 or 3 interactions with CLR. Therapeutic agents targeting the CLR-RAMP complexes have the potential to treat migraine headache, acute myocardial infarction, pulmonary hypertension, cancer, and several other disorders. In this study the PI proposes to elucidate the structural basis for RAMP modulation of CLR hormone selectivity by determining crystal structures of CGRP- and AM-bound CLR-RAMP heterodimers. The results will describe precisely how the hormones bind to their receptors and will aid the rational design of potent and selective therapeutic agents targeting the CLR-RAMP complexes.
Research Area	<b>Chemistry/Biochemistry</b>

Principal Investigator: <b>Ira Blader</b>	Project Title: <b>Role of PD-L1 in Ocular Toxoplasmosis</b>
Project Number: <b>HR11-010</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>5</b>	Year 1: \$37,460    Year 2: \$45,000    Year 3: \$45,000    Total: \$127,460
Research Summary	Toxoplasma gondii is one of the most prevalent pathogens in the world, primarily because after somebody is infected with Toxoplasma they remain infected. Although most infections are asymptomatic they can cause serious disease in immunosuppressed people, those infected congenitally, and in some cases otherwise healthy individuals. The retina is the most common tissue affected in the healthy individuals making Toxoplasma the most common infection of the retina. Once a Toxoplasma tissue cyst reactivates in the retina a properly regulated immune response is not mounted. Because the of body's improper immune response to the parasite, this infection is potentially blinding and thus must be treated properly. The objective of this project is to define how these retinal immune responses are regulated. The ultimate goal of this work is to develop better therapeutics to control Toxoplasma-induced eye damage.
Research Area	<b>Infectious Disease</b>

Principal Investigator: <b>Raphael Pinaud</b>	Project Title: <b>Estrogen-Modulation of Visual Processing and Plasticity</b>
Project Number: <b>HR11-175</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>6</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Humans are highly visual animals and loss of any visual function can severely impact quality of life. Visual problems are among the ten most prevalent causes of disability in America and can affect all populations at all ages. In children, visual problems can be congenital and are often associated with developmental delays requiring significant intervention. Similarly, adults (especially the elderly) whose vision is failing due to age, disease or injury have severely disrupted life styles and require special care. This places a significant burden on society to support those with impaired vision and much effort has been expended to alleviate visual deficits to improve quality of life. This research team will investigate the exciting hypothesis that the visual cortex can itself produce estrogen in a rapid and specific manner that can influence visual processing and plasticity, on a time-scale compatible with rapid neuromodulators. Such possibility may shed significant light on known deficits in visual perception that occur during menopause and anti-estrogen chemotherapies, and may initiate discussions on estrogen-replacement as a tool to shape visual perception. More broadly, these studies will reveal novel mechanisms that are important for visual function and for later improving clinical interventions to improve vision.
Research Area	<b>Neurobiology</b>

Principal Investigator: <b>Junping Chen</b>	Project Title: <b>Omega-3 and Cardiovascular Function in Pre-Diabetes</b>
Project Number: <b>HR11-156</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>7</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Pre-diabetes is a common disorder. Cardiovascular dysfunction (CVD), responsible for a majority of morbidity and mortality in diabetes, is assumed to develop in pre-diabetes stage. Studies have indicated that low-degree chronic inflammation is highly involved in CVD. This PI's preliminary data showed that serum levels of several inflammatory factors are altered. In addition, these factors are significantly associated with cardiovascular function. In this cohort study, the PI and her lab attempt to investigate for the first time that the effect of Omega-3 on inhibiting inflammation so as to improve insulin resistance and cardiovascular dysfunction in pre-diabetic women. Results from this study will contribute to the development of new treatment strategy on sub-clinical cardiovascular complications in pre-diabetes. Oklahoma has a very high population of pre-diabetes and diabetes, particularly among Native American and Hispanic populations. Thus outcome of current research study is likely to benefit these populations.
Research Area	<b>Instrumentation/Data Sciences/Clinical Evaluation</b>

Principal Investigator: <b>Leonidas Tsiokas</b>	Project Title: <b>Polycystin-Mediated Ca<sup>2+</sup> Signaling in the Primary Cilium</b>
Project Number: <b>HR11-109</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>8</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common genetic diseases affecting more than half a million Americans and 12.5 million people worldwide. Mutations in two genes, PKD1 and PKD2, are responsible for this debilitating disease. Their protein products, PKD1 and TRPP2, respectively, are plasma membrane-spanning proteins present in the primary cilium, a sensory-like organelle protruding from the cell surface. No effective treatments are currently available for ADPKD. This is due in part because of a gap in our knowledge of the normal function of PKD1 and TRPP2 at the cilium. This project will test the hypothesis that PKD1 and TRPP2 form a receptor-channel complex at the cilium activated by the secreted Wnt glycoproteins. If successful, these studies will not only advance the understanding of the pathophysiology of ADPKD, but they can also lead to the identification of potential target molecules against ADPKD.
Research Area	<b>Physiology/Pharmacology</b>
Principal Investigator: <b>Ted Bader</b>	Project Title: <b>Human Testing of Simvastatin for Chronic Hepatitis B</b>

Project Number: <b>HR11-035</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>9</b>	Year 1: \$44,288    Year 2: \$43,147    Year 3: \$42,400    Total: \$129,835
Research Summary	Hepatitis B virus (HBV) infects an estimated 400 million people, making it the most common chronic infectious disease worldwide. With complications from cirrhosis and cancer, HBV causes more than a million deaths per year. The therapy of HBV is sub-optimal. The treatment is not curative and requires long-term suppression with antiviral medicine to which the virus can quickly become resistant. Dr. Bader and his team have potentially discovered a new paradigm for anti-HBV treatment. They have found that simvastatin, a generic FDA-approved cholesterol-lowering drug, has robust anti-HBV activity in a standard human hepatoma cell line that has been used to discover all the currently FDA-approved anti-HBV drugs. Moreover, simvastatin is synergistic in combination with all the currently approved drugs. When tested alone with clinically relevant drug-resistant strains, simvastatin has the same antiviral activity as against the wild-type strain. The benefits the PI seeks for the state of Oklahoma are: one, to obtain sponsorship of research to employ research staff; two, improve the care of hepatitis B infection in those citizens they evaluate as possible subjects; three, sell an initial license to the intellectual property; and four, secure royalty commitment in the event of future commercial success. These benefits will support and further the mission of the PI's university as it endeavors to improve the health care for all Oklahomans.
Research Area	<b>Physiology/Pharmacology</b>

Principal Investigator: <b>Carol Dionne</b>	Project Title: <b>Work Task Performance Measures in Amputees with TTAT</b>
Project Number: <b>HR11-097</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>10</b>	Year 1: \$32,699    Year 2: \$34,146    Year 3: \$36,679    Total: \$103,524
Research Summary	Trans-tibial amputation (TTAT) is the most frequent type of lower limb amputation surgery due to a traumatic event. Despite advances in rehabilitation and prosthetic technology, Oklahomans with TTAT struggle with job re-entry and retention. Too often, workers with TTAT sustain painful injury while using the prosthetic limb and performing work-related activities, precluding them from continual employment. Mechanisms of musculoskeletal residuum pain and debilitating injury in working Oklahomans with TTAT are not well understood. A translational, contextual examination is required to study mechanical loads and muscle activity within the prosthetic socket during actual work-related activity and quantify the presence of bone loss and inflammation in the residuum. Results from this innovative approach will not only serve to isolate unwanted forces that may be addressed in future rehabilitative approaches and prosthetic designs and adjustment, but also will inform comparative and longitudinal studies in amputation rehabilitation.
Research Area	<b>Instrumentation/Data Sciences/Clinical Evaluation</b>
Principal Investigator: <b>Anna Csiszar</b>	Project Title: <b>Novel Mechanisms of Vascular Aging</b>

Project Number: <b>HR11-084</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>11</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	The research proposed in this application is innovative because it focuses on an entirely novel mechanism underlying the increased cardiovascular mortality and morbidity in the elderly: age-related impairment of master regulator of cellular redox homeostasis. The research also assesses a novel target for vasoprotection and prevention/treatment of cardiovascular diseases. The contribution of the proposed research is expected to be the identification of the key age-related endocrine mechanisms, age-related IGF-1 deficiency, that regulate vascular oxidative stress resistance. Alterations in these regulatory factors exacerbate oxidative stress-induced vascular impairment and contribute to the development of age-related cardiovascular diseases. The significance of the proposed mechanistic studies is supported by results of several large-scale clinical studies, including the Framingham Heart Study and the Cardiovascular Health Study, all of which show a strong association between low levels of circulating IGF-1 and a significantly increased risk of cardiovascular and cerebrovascular mortality and morbidity in the elderly. This research team proposes to use innovative approaches, combining studies conducted in vivo and ex vivo with experiments using a novel mouse model of endocrine IGF-1 deficiency. Preliminary studies strongly suggest that this approach will enable the team to identify novel pathways involved in vascular aging.
Research Area	<b>Physiology/Pharmacology</b>

Principal Investigator: <b>Robert Alderson</b>	Project Title: <b>Competing Core Processes in ADHD</b>
Project Number: <b>HR11-034</b>	Organization: <b>Oklahoma State University</b>
Rank: <b>12</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	The proposed study will be the first to experimentally examine opposing predictions stemming from the functional working memory and behavioral inhibition models of ADHD, and consequently improve identification of potential core deficits of the disorder. The core deficit approach is particularly advantageous to the examination of ADHD because it holds considerable promise for the eventual development of more objective neurocognitive diagnostic procedures with improved predictive power relative to current best practices. Interventions that effectively improve identified underlying core deficits are likely to positively affect secondary, behavioral symptoms of the disorder (i.e., inattentive, hyperactive, and impulsive behavior), and once developed hold considerable promise for promoting long-term treatment gains. Consequently, effective treatment and prevention of ADHD is dependent upon a comprehensive understanding of its underlying mechanisms and core features.
Research Area	<b>Nutrition/Psychology/Public Health</b>

Principal Investigator: <b>William Sonntag</b>	Project Title: <b>IGF-1 and the Genesis of Late-life Depression</b>
Project Number: <b>HR11-075</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>13</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Depression in older adults is an under-recognized and under-treated medical condition. Moreover, there are many older patients with subclinical depression who are at increased risk for major depression. Geriatric depression significantly reduces average life expectancy and antidepressant treatment is less effective than in younger patients, suggesting that depression in the elderly has a unique etiology. Recently the concept has emerged that age-related alterations in trophic factors and circulating hormones influence depression in the elderly. Insulin-like growth factor I (IGF-1) is an important trophic factor that confers important neuroprotective effects, decreases with age and has role in age-related structural and functional alterations in the brain. The goal of this application is to investigate the cellular and molecular mechanisms that contribute to depression in elderly individuals and determine the mechanisms through which IGF-1 alleviates the disease. This information would then be used to develop therapeutic interventions to alleviate depression in the elderly.
Research Area	<b>Neurobiology</b>

Principal Investigator: <b>William McShan</b>	Project Title: <b>Mobile Element SpyCIM1 Enhances Survival in <i>S. pyogenes</i></b>
Project Number: <b>HR11-133</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>14</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Infections by <i>Streptococcus pyogenes</i> are a major health problem in Oklahoma and worldwide. The proposed project will examine the role of chromosomal island SpyCIM1 in promoting survival, virulence, and spread to new populations of this pathogen. The preliminary studies by the PI show that SpyCIM1 causes a growth-dependent mutator phenotype in <i>S. pyogenes</i> that allows the organism to rapidly acquire antibiotic resistance and other genetic changes. This project will focus on two areas of investigation: the regulation of multiple drug resistance pump LmrP by SpyCIM1 and the mechanism for dissemination of SpyCIM1 to new hosts. The members of the SpyCIM1 family of chromosomal islands are common in <i>S. pyogenes</i> , and we are just beginning to understand their impact on virulence. The proposed work could lead to fundamental advances in our knowledge of <i>S. pyogenes</i> genetics and virulence as well as lead to improved patient management and treatment strategies.
Research Area	<b>Infectious Disease</b>

Principal Investigator: <b>Chuanbin Mao</b>	Project Title: <b>Bifunctional Phage Particles for Targeted Cancer Therapy</b>			
Project Number: <b>HR11-006</b>	Organization: <b>University of Oklahoma</b>			
Rank: <b>16</b>	Year 1: \$45,000	Year 2: \$45,000	Year 3: \$45,000	Total: \$135,000

Principal Investigator: <b>Junpeng Deng</b>	Project Title: <b>Structure Function Studies on ROC Dimeric GTPase</b>			
Project Number: <b>HR11-118</b>	Organization: <b>Oklahoma State University</b>			
Rank: <b>15</b>	Year 1: \$45,000	Year 2: \$45,000	Year 3: \$45,000	Total: \$135,000
Research Summary	<p>Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common cause of Parkinson's disease (PD). There is a critical need to better understand the enzymatic and regulatory mechanisms of LRRK2 to elucidate its roles in PD development. The focus of this proposal is on providing further structural insights into the multi-domain organization in LRRK2, and the enzymatic mechanism of the ROC GTPase domain. The research team proposes to use a combination of biochemical and biophysical methods including x-ray crystallography to: 1) determine the ROC-COR tandem domain of LRRK2; and 2) determine the mechanism of ROC guanine nucleotide exchange facilitated by ARHGEF7. Their studies will open up new opportunities and provide a platform for designing selective inhibitors/activators that may in their turn be further developed into new therapeutics against PD. This research is closely relevant to OCAST's mission to help promote better human health and longer life-span in the state.</p>			
Research Area	<b>Chemistry/Biochemistry</b>			

Research Summary	The assembly of tubulins is important for normal cell division. It has been demonstrated that conventional tubulin-binding anti-cancer drugs work by one of two ways; one is to bind to free tubulins to prevent them from being assembled into microtubules (for drugs such as colchicine) and another is to bind to assembled tubulins (i.e., microtubules) to stabilize them and thus prevent them from being disassembled into free tubulins (for drugs such as paclitaxel). This project will make a non-toxic biomolecular rod-like nanoparticle, called phage, bifunctional through genetic engineering: its side wall is made of thousands of tubulin-interacting sites for inhibiting normal tubulin assembly while its tip is composed of multivalent cancer cell-recognizing peptide motifs for targeting breast cancer cells. This bifunctional bio-particle will be able to target cancer cells, inhibit cell division and induce cancer cell death. Therefore, this project will develop a new type of targeted cancer therapeutics.
Research Area	<b>Biomedical Engineering</b>

Principal Investigator: <b>Christopher Sansam</b>	Project Title: <b>The Role of TICRR in the Human DNA Damage Response</b>
Project Number: <b>HR11-022</b>	Organization: <b>Oklahoma Medical Research Foundation</b>
Rank: <b>17</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Commonly used cancer treatments block DNA replication and damage DNA, thereby killing both cancer cells and healthy proliferating cells alike. All cells are partially protected from these cytotoxic chemotherapies through DNA damage response signaling pathways that pause cell division and enable DNA repair. Nearly all cancer cells have a partially impaired DNA damage response, so inhibition of the DNA damage response has the potential to sensitize cancer cells to chemotherapy treatment. This could enable the use of higher doses of cytotoxic chemotherapies with reduced side effects. Broadly, this study aims to reveal how cells replicate DNA and respond to DNA damage so that the research team may develop effective chemotherapy sensitizers. As part of their efforts to understand the mechanisms of the DNA damage response and DNA replication, the team has identified an uncharacterized protein called TICRR which is required for both DNA replication and the DNA damage response. In these studies the research team will elucidate how TICRR acts with other proteins in protecting cells from replication inhibition or DNA damage. They anticipate that through revealing the mechanisms of these processes, they will enable the development of better cancer therapies.
Research Area	<b>Cell/Molecular Biology</b>

Principal Investigator: <b>Shannon Conley</b>	Project Title: <b>An Experimental Bi-Modal Treatment Strategy for Glaucoma</b>
Project Number: <b>HR11-169</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>18</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	The goal of this program is to develop a current compacted DNA nanoparticle-based gene therapy technology for the treatment of glaucoma-associated retinal degeneration. Glaucoma is a non-monogenic degenerative disease affecting ~2.2 million people in the United States. In spite of the existence of pharmacotherapies for controlling glaucoma progression, no treatments currently exist for glaucomatous retinal degeneration or the blindness associated therewith. The PI has previously utilized a retinitis pigmentosa model to demonstrate the utility of these nanoparticles for the treatment of inherited retinal diseases. In this application the PI proposes to apply knowledge obtained from these preliminary studies to studies using nanoparticles to overcome the devastating loss of vision phenotype in a model for glaucoma, the second leading cause of blindness worldwide. The technology to be used can unimolecularly compact DNA with lysine polymers substituted with polyethylene glycol (PEG) into neutral charge nanoparticles with radii of ~8 nm. These particles can penetrate the cell membrane via nucleolin receptor associated endocytosis and cross the nuclear membrane pore to the nucleus within 15 minutes. The potential scientific and clinical benefits of these proof-of-principle glaucoma studies are substantial.
Research Area	<b>Physiology/Pharmacology</b>

Principal Investigator: <b>Zoltan Ungvari</b>	Project Title: <b>Novel Strategy for Neuroprotection in Neonatal Stroke</b>
Project Number: <b>HR11-083</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>19</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	Hemorrhagic stroke is a major complication of prematurity. Affecting 12,240 infants per year in the USA, this complication exposes them to the development of hydrocephalus, cerebral palsy, and mental retardation. Clinical strategies to prevent or minimize post-hemorrhagic brain damage are currently inadequate and largely unsuccessful. The long-term goal of this project is to develop novel therapeutic approaches for neuroprotection in infants with neonatal stroke targeting intrinsic antioxidant response pathways. The objective of the present proposal is to develop a new fusogenic liposome-based delivery system for resveratrol to be used for pharmacological neuroprotection in a pre-clinical model of neonatal stroke. The central hypothesis is that fusogenic liposome-derived resveratrol will induce Nrf2-driven cytoprotective pathways in the neurons, which will mitigate oxidative stress-induced cellular injury and thereby prevent permanent brain damage.
Research Area	<b>Biomedical Engineering</b>

Principal Investigator: <b>William Rodgers</b>	Project Title: <b>Cytoskeletal Regulation of Raft Structure and Function</b>
Project Number: <b>HR11-042</b>	Organization: <b>Oklahoma Medical Research Foundation</b>
Rank: <b>20</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	<p>Membrane raft microdomains are a fundamental property of cell membranes. Nevertheless, how rafts are formed and maintained is not understood. The PI seeks to elucidate these properties in this project. This information will impact the understanding of human diseases whose progression or prevention is mediated by rafts. Knowledge regarding rafts will be important for identifying new avenues for treatment of these diseases. Examples of these diseases and their association with rafts are the following:</p> <ol style="list-style-type: none"> <li>1. Infectious diseases, because rafts are the site of entry and exit of many viruses and bacteria;</li> <li>2. Autoimmune disorders, because rafts are critical for proper regulation of immune cells;</li> <li>3. Diabetes, because rafts are essential for activation of insulin signaling;</li> <li>4. Alzheimer's disease, because rafts are the site of protein processing that leads to senile plaques containing amyloid-<math>\beta</math>-peptide;</li> <li>5. Atherosclerosis, because rafts host signals that activate development of atherosclerotic lesions.</li> </ol> <p>In summary, this research will provide novel insight into a biologically challenging question, namely, how raft microdomains are established and maintained. The findings will show new mechanisms by which the cytoskeleton impacts cellular signaling. This knowledge will assist in designing new strategies to treat diseases that arise from Lck upregulation, which includes certain malignancies and autoimmune diseases.</p>
Research Area	<b>Cell/Molecular Biology</b>

Principal Investigator: <b>Wendy Picking</b>	Project Title: <b>TTSS Proteins as Protective Antigens Against Salmonella</b>
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Principal Investigator: <b>Marie Hanigan</b>	Project Title: <b>Gamma-Glutamyl Transpeptidase and Cardiovascular Disease</b>
Project Number: <b>HR11-085</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>21</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The enzyme gamma-glutamyl transpeptidase (GGT1) is elevated in the serum of patients with cardiovascular disease and is expressed by the macrophage-derived foam cells within human atherosclerotic plaques. The hypothesis to be tested in this proposal is that GGT activity on the surface of the foam cells within the plaque has a major role in plaque progression. The data from these studies will clarify the relative contributions of GGT1 and GGT5 to the metabolism of leukotrienes in human atherosclerotic plaques. The data will directly evaluate the effect that expression of these enzymes has on signaling through CysLT1. These studies may provide novel insight into the resistance of mice to the development of atherosclerosis and lead to development of new mouse models of atherosclerosis that more closely reflect the development of human disease. In addition, this work has the potential to lead to new mouse models of atherosclerosis, biomarkers for susceptibility to atherosclerotic disease and new targets for therapeutic intervention in the disease process.
Research Area	<b>Cardiovascular Disease</b>

Principal Investigator: <b>Franklin Hays</b>	Project Title: <b>hENT Drug Transport in Cancer Therapy</b>
Project Number: <b>HR11-046</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>22</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	Studies outlined within this proposal seek to define molecular determinants of drug disposition and response in the treatment of human cancer. The PI's primary near-term focus is characterizing human Equilibrative Nucleoside Transporter (hENT) drug recognition and transport using structural biology and functional assays. This coupled approach allows one to relate sequence elements and motifs to structural outcomes in developing a molecular model of transporter function. Sequence-function relationships will facilitate clinical screening of hENT genotypes that are resistant to chemotherapeutics while structure-function relationships will guide future drug development and therapeutic design. These insights are of paramount importance since hENT expression level and activity has been directly linked to chemotherapeutic outcomes in the treatment of human cancer. Thus, understanding how hENT functions at the molecular level will provide direct inroads into guiding clinical treatment decisions for Oklahomans facing a cancer diagnosis.
Research Area	<b>Chemistry/Biochemistry</b>

Project Number: <b>HR11-203</b>	Organization: <b>Oklahoma State University</b>
Rank: <b>23</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	While vaccination has perhaps been the most broadly powerful disease prevention approach in modern medicine, the continued transmission of infectious diseases in the US and in developing nations underscores the urgent need for more effective vaccines. Currently, diarrheal diseases caused by microbial infection disproportionately affect children and the immunocompromised. Standard live, attenuated bacterial vaccine strains are either ineffective or are too dangerous for these populations. The PI and her lab propose the use of bacterial proteins as a vaccine against infection by <i>Salmonella</i> spp, which cause gastroenteritis ranging from self-limiting to severe and deadly.
Research Area	<b>Infectious Disease</b>

Principal Investigator: <b>James McGinnis</b>	Project Title: <b>Nanoceria Protect Rods and Cones in Degenerating Retinas</b>
Project Number: <b>HR11-004</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>24</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	Retinitis pigmentosa (RP) is a family of orphan diseases that cause hereditary rod and cone photoreceptor degeneration and eventually blindness. Currently there are no effective therapeutic treatments. Oxidative stress is a common upstream node for all forms of RP irrespective of the primary genetic defect. The PI previously demonstrated that cerium oxide nanoparticles (nanoceria) are potent regenerative antioxidants which reduce oxidative stress and prevent light-induced blindness in rats. Recently, he showed that nanoceria eliminate pathologic neovascularizations in a mouse model for AMD and prolong vision in a mouse with inherited retinal degeneration. The PI now hypothesizes that nanoceria will protect rods and cones in a rat model that recapitulates a form of autosomal dominant RP. The data from these studies will form the basis for FDA approval of nanoceria as an Investigational New Drug (IND) and the extension of their therapeutic use in humans for AMD and diabetic retinopathy.
Research Area	<b>Neurobiology</b>

Principal Investigator: <b>Amanda Morris</b>	Project Title: <b>Promoting Mental Health in High-Risk Adolescent Girls</b>
Project Number: <b>HR11-130</b>	Organization: <b>Oklahoma State University-Tulsa</b>
Rank: <b>25</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	This project will examine whether adolescent emotions in daily life influence the development of adolescent depression, substance use, and risky sexual behavior among high-risk girls living in the Tulsa area. The study will also investigate whether positive parent-child and peer relationship qualities serve as protective factors for at-risk girls. As such, this study will inform social scientists, policy makers, practitioners, and interventionists regarding potential causes of and treatment for depression and related risky behavior. Given the costs of adolescent mental health to families, communities, and states, further research of adaptive and maladaptive pathways among adolescent girls is needed.
Research Area	<b>Nutrition/Psychology/Public Health</b>

Principal Investigator: <b>Miao Zhang</b>	Project Title: <b>Role of AMP-Activated Protein Kinase in Atherosclerosis</b>
Project Number: <b>HR11-205</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>26</b>	Year 1: \$45,000   Year 2: \$45,000   Year 3: \$45,000   Total: \$135,000
Research Summary	Atherosclerosis is the leading cause of morbidity and mortality in Western populations. The proposed project will study the effects of AMP-activated protein kinase (AMPK) $\alpha 1$ on development of atherosclerosis. The in vivo and in vitro studies will explore the role of AMPK $\alpha 1$ in monocyte-macrophage cells, which are crucial in the initiation, progression, and development of atherosclerotic plaques. This study will advance our understanding of how AMPK regulates macrophage cholesterol homeostasis and foam cell formation. Therefore this project may result in novel therapeutic targets in the management of atherosclerotic cardiovascular disease.
Research Area	<b>Physiology/Pharmacology</b>

Principal Investigator: <b>Yingmei Liu</b>	Project Title: <b>An Ultra-Precise Bio-magnetic Scanning Microscope</b>
Project Number: <b>HR11-090</b>	Organization: <b>Oklahoma State University</b>
Rank: <b>27</b>	Year 1: \$44,800    Year 2: \$44,800    Year 3: \$44,800    Total: \$134,400
Research Summary	The proposed magnetic scanning microscope can detect tiny magnetic variations, and thus reveal the presence of cardiac dysfunctions, make inferences about neural activity inside brains, and detect threats to human health. It can scan brains and hearts, and localize abnormal regions before surgical removal. This could greatly shorten the length of a diagnostic process. The proposed magnetic microscope could provide a reproducible and unbiased determination of a new drug's performance between baseline investigations and follow-up investigations. This is extremely critical for correctly approving the drug. The magnetic microscope could also be a safer and more precise alternative for a magnetic resonance imaging (MRI) scanner. The long-term goal is to implement a low-cost and portable ultra-precise magnetic scanning microscope, and apply it into widespread medical uses, especially in magnetoencephalography and magnetocardiography. This will combine existing technology from ultracold quantum gases and health research in a completely unique way.
Research Area	<b>Biomedical Engineering</b>

Principal Investigator: <b>Daqing Piao</b>	Project Title: <b>Photonic-needle Assessment of Hepatic Steatosis</b>
Project Number: <b>HR11-043</b>	Organization: <b>Oklahoma State University</b>
Rank: <b>28</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	This research aims to develop and evaluate a technology for rapidly assessing the intensity of liver steatosis (fatty change), and reliably discriminating the macro-steatosis (single large lipid droplet in a hepatocyte) from the micro-steatosis (numerous small lipid droplets in a hepatocyte). Such technologies are urgently needed for liver transplantation but do not exist clinically. Liver transplantation programs, including those renowned centers in Oklahoma, increasingly use livers of "marginal" quality such as fatty livers. Macro-steatosis in the donor organ represents a major risk to organ recipients. Micro-steatosis, on the other hand, is not associated with an increased risk of dysfunction. This research develops an ultra-fine photonic-needle sensing approach that integrates optical reflectance spectroscopy and low-coherence interferometry to quantify the volume-content and size-distribution of lipid droplets in liver tissue for instantaneous, pre-operative graft analysis. Such technology helps hepatic surgeons determine if an available organ is within a safe steatosis range.
Research Area	<b>Transplantation</b>

Principal Investigator: <b>Jian Xu</b>	Project Title: <b>Diabetes, 26S Proteasomes and Caloric Restriction</b>
Project Number: <b>HR11-200</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>29</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The proposed project seeks to test the hypothesis that 26S proteasome activation is an early event in promoting diabetes-promoted inflammatory response which can be mitigated by caloric restriction (CR) through 26S proteasome inhibition. The PI expects that the project will (1) help to resolve the controversy over 26S proteasome functionality in diabetes and therefore to better understand the disease; (2) identify a novel mechanism of 26S proteasome modulation (via CR's inhibitive effect) so that the therapeutic potential of CR can be further exploited in treating diabetes. Since proteasome inhibition (with inhibitor administration) is a recent FDA-approved therapeutic regimen for cancer, the present study may bear promise of treating diabetes with this regimen through CR; and (3) discover a new mechanism underlying CR's anti-inflammatory effect which justifies further investigation on CR's potential of improving conditions in diseases (diabetes, obesity, hypertension, and atherosclerosis) and ageing that are associated with enhanced inflammatory response.
Research Area	<b>Physiology/Pharmacology</b>

Principal Investigator: <b>Karla Rodgers</b>	Project Title: <b>Mechanisms to Regulate VDJ Recombination upon DNA Damage</b>
Project Number: <b>HR11-053</b>	Organization: <b>University of Oklahoma Health Sciences Center</b>
Rank: <b>30</b>	Year 1: \$45,000    Year 2: \$45,000    Year 3: \$45,000    Total: \$135,000
Research Summary	The V(D)J recombinase, consisting of the RAG1 and RAG2 proteins, is essential for development of the adaptive immune system; however, errors in its DNA recombination activity can result in genomic instabilities leading to increased risks of lymphoid malignancies. New data indicate the V(D)J recombinase is sequestered from the genome upon exposure to DNA damaging agents in a possible attempt to reduce aberrant recombination reactions under certain conditions. The goal of this study is to determine the mechanistic basis for this effect. This project will open a new paradigm in the regulation of V(D)J recombination activity, specifically during times of genotoxic stress. The outcome of this study may provide a useful diagnostic tool in assessing the robustness of DNA repair in developing lymphoid cells. In the long term, this study may lead to treatments that reduce risks of leukemia or lymphomas in patients treated with DNA damaging therapies.
Research Area	<b>Immunology</b>

# OKLAHOMA HEALTH RESEARCH PROGRAM FY11 FUNDING REVIEW

## APPLICANT INFORMATION

**Application Preparation Workshops held:** Oklahoma City, Stillwater, Tulsa

**Total Workshop Attendance:** 28

**Statements of Intent Received:** 220

**Applications Received:** 168

**Resubmissions Received:** 27      **Resubmissions Approved:** 21      **Resubmissions Funded:** 2

**Amount Requested, First Year:** \$7,447,845      **Total Amount Requested:** \$21,620,622

## APPLICANT ORGANIZATIONS

Brindis, LLC	1
Cotten Robotics, Inc.	1
Healthy Lifestyles in Aging, Inc.	1
Laureate Institute for Brain Research	3
Oklahoma Medical Research Foundation	13
Oklahoma State University	37
Oklahoma State University - Tulsa	4
Oklahoma State University - University Multispectral Laboratories	1
Oklahoma State University Center for Health Sciences	9
Southeastern Oklahoma State University	1
Southwestern Oklahoma State University	1
Thomas Lynn Institute for Healthcare Research	2
University of Central Oklahoma	2
University of Oklahoma	16
University of Oklahoma - Tulsa	1
University of Oklahoma Health Sciences Center	71
University of Tulsa	3
Veterans Research & Education Foundation	1