HSC IACUC Meeting Minutes for Thursday, July 11, 2019
Meeting Place – [redacted]
Meeting time - 12:19 pm – 1:18 pm

Members Present
Attending Veterinarian
BHC Representative (NV)
Chair
IACUC Administrator (NV)
Member #8
Member #18
Member #20
Member #22
Member #23
Member #24
Member #25
Member #27
OACC Operations Manager, Recording Secretary (NV)
SRS Rep (NV)

Members Absent
ARF Representative (NV)
EOHS Representative (NV)
Member #11
Member #12 (Vice-Chair)
Member #17
Member #26
Radiation Safety Representative (NV)

NV= non-voting members, consultant or staff

Per the request of the Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 10.

Item # 1: Approval of Agenda:
A motion for approval of the July 11, 2019 agenda was made and carried. The agenda was approved as presented.
Decision: Approved: Yes=10 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes from Thursday, June 6, 2019 meeting:
A motion for approval of the June 6, 2019 meeting minutes was made and carried. The PI lab name was removed from protocol 200884 on page 4. The minutes were approved as amended.
Decision: Approved: Yes=10 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200287 Minor - "*M. tuberculosis* pathogenesis in mouse aerosol model of infection."
Reviewers: *Chair, AV*
Summary: We are adding two of our newest strains, LysMCre-Atg9 fl/fl & Ubc-Cre-Atg9 fl/fl, to our working protocol.
Approved by IACUC Chair and Attending Vet on 7/3/2019.

200423 Major DMR – "Study of papillomavirus entry and infection in mouse models."
Reviewers: *17, 25, AV*
Summary: We would like to (1) test a potential prophylactic agent (FDA approved in humans), (2) include another means of tissue wounding (at a different tissue site) for analysis of papillomavirus infections, (3) test sex hormone effects in PV infections. Additional numbers of mice will be needed to carry out this work.
Sent for DMR #2 on 6/26/2019. Waiting for updated animal numbers table.

200767 DMR - "Treatment of the rat malignant brain tumor."
Reviewers: *17, 25, AV*
Summary: Malignant glioma is the most common type of brain cancer. Brain cancer forms a specific environment that has low in oxygen. This environment supports cancer survival, migration, and resistance to the therapy. Several studies show that the increase of oxygen delivery to tumor decreases its survival and growth. We suggest drag reducing polymers (DRP) as a treatment that changes the cancer environment by increasing oxygen delivery. In our previous research, we have shown the improvement of oxygen delivery to the rat brain after traumatic brain injury or stroke. In this pilot study, we will transplant brain cancer cells (C6 rat glioma) into the rat brain. After that, the animals will be treated for 4 weeks with DRP. During this period, we will monitor the tumor growth by magnetic resonance imaging (MRI). We think that DRP will reduce tumor growth.
Approved as a DMR by Sub-Committee on 6/11/2019.

200894 3-yr RW DMR - "Effect of intermittent hypoxia on renal function in rats."
Reviewers: *12, 27, AV*
Summary: This study will focus on renal (kidney) response and it's functioning during chronic kidney disease (CKD) especially during the co-existing condition of sleep apnea (bouts of low oxygen concentration experienced in the body during sleep). There are various conditions that may cause a person to become susceptible to sleep apnea. It is common among CKD patients to also develop sleep apnea as a co-existing condition. It is imperative to protect renal function in these patients to preserve quality of life and to delay or prevent kidney transplant.
In order to study CKD, an oral gavage of adenine will be administered to Sprague Dawley to induce moderate renal failure within 3-5 days. These animals will be exposed to chronic intermittent hypoxia (CIH) by simulation method. This study will evaluate the effect of sleep apnea with normal or impaired kidney function to determine if sleep apnea alone or in combination with preexisting renal impairment leads to further declines in renal function as stated in the project overview. Renal function will be evaluated by determining glomerular filtration rate and blood samples will be collected to measure blood urea nitrogen (BUN), plasma creatinine, plasma glucose, and hematocrit.

In order to collect urine samples from study animals and thus measure GFR, metabolic cages will be utilized whereby animals will be single-housed in special caging that is designed to collect urine samples. Urine will be collected for a 24-hour period.
CKD study will incorporate macitentan, an effective blocker of endothelin receptors that play a role in the regulation of blood pressure in the body. Its administration will shed light on its effects on resulting blood pressures from CKD and CIH treatments together and alone.
This study also investigates the relation of the immune system and hypertension, specifically if the immune system is involved in the development of hypertension driven by the condition of sleep apnea. Chloroquine is an effective immunosuppressant and will be used in this study aid in showing the effect that immune system development may or may not have on the manifestation of hypertension during CIH treatment.
Blood pressure measurement will be obtained by using indwelling telemetry devices that require surgical implant. Telemetry devices allow for continuous recording of blood pressure, activity, and heart rate data during the animals awake and sleep cycles and will be recorded 72 hours per week of treatment.
These studies will aid in providing insight into the rationale for aggressive in patients with both sleep apnea and chronic kidney disease.
We completed in vivo studies in untreated, Sham and IH rats. This coming year we will complete any additional studies requested by reviewers and others to collect tissues to evaluate the role of renal H_2S production in protecting the kidney from IH-induced renal damage. Currently then, we are requesting to keep this protocol open in the event that we will need to complete additional studies as aforementioned. At this time, we will request no animals allotted unless needed in the future.
Approved as a DMR by Sub-Committee on 6/10/2019.

200919 3-yr RW DMR - "Remodeling of blood-brain barrier & cell death after stroke in Rats."
Reviewers: *11, 24, AV*
Summary: Currently, treatment options for ischemic stroke are very limited and new approaches to treatment and medical care are urgently needed. However, only recombinant tissue plasminogen activator (rtPA) is FDA approved for the treatment of ischemic stroke, and it must be given within 4.5 hours after stroke onset, which limits its use to less than 5% of stroke victims. Our research is focused on novel neurorestorative approaches that could be given beyond the early phase of stroke, since the time window for improving recovery is far longer. In particular, we are trying to characterize cellular and molecular events in response to stroke to identify novel treatment strategies that could promote functional neurovascular remodeling to improve outcome in patients.
We have begun to identify some recovery factors. For instance, we found newly formed vessels in brain tissue 3 weeks after experimental stroke in rats. These new vessels have high blood flow and blood-brain barrier (BBB) permeability. We have been investigating if 1) drugs to promote vessel growth could be used to facilitate restoration of BBB properties; 2) by taking advantage of the immature vasculature, compounds that cannot normally cross an intact BBB into brain tissue could be used to promote functional vessel and brain cell regrowth. We will also test if combining treatment of drugs to limiting brain damage during acute stage with the administration of drugs to promote vessel growth during recovery will result in additive effects on functional neurovascular remodeling. The focus of our proposal is to use innovative treatment strategies in an animal model of stroke and to monitor their effects dynamically with MRI. It is

our goal to 1) characterize the spatiotemporal profiles of neurovascular remodeling events following stroke; and 2) identify the time window for therapies aimed at improving functional neurovascular remodeling to aid in recovery. These experiments will provide critical preclinical information that may elucidate neurovascular recovery and guide therapeutic strategies to promote stroke outcome in human patients. In addition, the research, longitudinal monitoring of microglial activation after stroke with SPION-enhanced MRI, will provide a novel experimental approach for monitoring the progression and treatment of stroke and other neurodegeneration disorders in support of direct subsequent applications in the clinic. In addition, the proposed studies will enhance our understanding of the functional alteration of microglia and the role of the key inflammatory events in neurovascular remodeling following stroke.
Approved as a DMR by Sub-Committee on 6/10/2019.

200925 3-yr RW DMR - "Molecular Regulation of Stem Cell and Cancer Cell Mobilization, Homing and Engraftment with the Bone Marrow using Mouse Models."
Reviewers: 11, 24, AV
Summary: Hematopoietic stem and progenitor cell (HSPC) transplantation is a critical therapy for the treatment of blood cancers such as leukemia, lymphoma and myeloma, as well as some autoimmune and cardiac diseases. To isolate HSPCs for clinical use, patients are treated with drugs that cause the release of HSPCs from their location in the bone marrow into the peripheral blood, which can be isolated with relative ease. This process is called mobilization and the use of mobilized HSPCs is replacing the more invasive bone marrow punctures used previously in the clinic. In order to improve the number of HSPCs isolated, especially for those patients who are "poor mobilizers", our laboratory is interested in studying the molecules that regulate this process of HSPC release into the bone marrow. By treating the animals with mobilization agents, we can assess the ability of HSPCs to mobilize from the bone marrow and into the blood. We also use these techniques to isolate HSPCs from donor mice, which are then used in transplantation experiments into recipient mice. These studies allow us to measure stem cell fitness.
Once the HPSCs have been "mobilized" and isolated, they are transplanted into the blood of the recipient patient, after which, the HSPCs must migrate through the blood stream and find their way back into the bone marrow of the patient. Once in the bone marrow, these cells can then proliferate and differentiate to replenish the blood and immune cells, which have been destroyed by chemotherapies. This process of migrating from the peripheral blood back to the bone marrow is called "homing" and the process of long term cellular replacement of the bone marrow is called "engraftment." Unfortunately, homing is an inefficient process, which often leads to patients requiring multiple rounds of HSPC transplants. Our lab is also very interested in identifying molecules involved in the homing of transplanted HSPCs from the blood back into the bone marrow. Following HSPC isolation and transplantation into recipient mice, we can measure the ability of HSPCs to home to the bone marrow and also engraftment or repopulate the blood immune system of the irradiated recipient mice. More recently, studies have shown that diabetes impairs HSPC mobilization, homing, and engraftment which is an additional link that we are interested in evaluating using our mouse models.
Furthermore, leukemic stem cells (LSC) and ovarian cancer (OvCa) cells can utilize very similar mechanisms to migrate to and engraft within the bone marrow of a patient. Once engrafted in the bone marrow, LSCs and OvCa cells become difficult to target with various chemotherapies. As such, identifying mechanisms to release LSC and OvCA cells from the protective environment of

the bone marrow would greatly impact treatments for both blood and solid tumor patients. By adoptively transferring human OVCA cells into immunocompromised mice, we can begin to determine whether these cells can migrate to and are maintained within the bone marrow microenvironment. We can also use specific chemotherapy agents to determine if these drugs can access the often quiescent cells within the mouse bone marrow.
The overall goals of this project are to study the molecules on the surface of the HSPCs, LSCs and OvCa cells that communicate with the bone marrow and evaluate how these molecules regulate both the processes of mobilization, homing, engraftment, proliferation, quiescence, and disease relapse. These studies will lead us to greater insights into the role of signaling and adhesion molecules in HSPC, LSC, and OvCa cell communication with the bone marrow. Furthermore, this understanding will likely lead to new targets for therapeutics that can 1) modulate HSPC isolation and transplantation, which is critical for more effective patient treatment; and 2) regulate the release of LSC and OvCa cells from the BM, which will improve current chemotherapeutic treatments and likely reduce relapse.
Approved as a DMR by Sub-Committee on 6/17/2019.

200932 3-yr RW DMR - "Neurochemical, electrophysiological and behavioral studies of a rat model of prenatal ethanol exposure."
Reviewers: *22, 8, AV*
Summary: Our research addresses the question of whether the consumption of moderate amounts of ethanol by mothers while they are pregnant causes long-term functional consequences in the offspring's brain. Using a rat model of prenatal ethanol exposure, we have observed that the consumption of moderate quantities of ethanol during pregnancy can cause subtle but persistent neurochemical changes in the brain of offspring. These changes occur in specific brain regions involved in the consolidation of short term memory into long term memory, both in rats and in humans. The neurochemical alterations caused by prenatal ethanol exposure decrease activity-dependent enhancement of synaptic communication between neurons leading to functional deficits in these brain regions. We believe that these changes may contribute to the learning disabilities observed in children whose mothers drank during pregnancy. Our current studies include preclinical screening of putative therapeutic agents for treating prenatal alcohol-induced learning deficits, and the development of novel biomarkers for the early detection of prenatal alcohol-induced functional brain damage.
To address these objectives, we will examine the long-lasting neurophysiological and behavioral consequences of moderate prenatal alcohol exposure on affected adult offspring. We will conduct electrophysiological studies of hippocampal and medial frontal cortical brain activity and correlate prenatal alcohol-induced alterations in brain physiology with alterations in behavioral performance using behavioral paradigms known to be sensitive to functional damage to these two brain regions. Subsequently, we will examine whether drugs that specifically target the histaminergic neurotransmitter system which we have established as altered in prenatal alcohol-exposed offspring, can ameliorate the physiological and behavioral deficits we have observed in prenatal alcohol-exposed rats. The goal of these studies is to establish a preclinical rationale for considering the use of these drugs in adolescents with FASD.
Approved as a DMR by Sub-Committee on 6/20/2019.

Item # 4 New Protocols:

200901 DMR - "SerpinB13 knockout mouse strain characterization."
Reviewers: *18, 8, AV*
Summary: We have a growing colony of serpin B13-deficine mice at UNM call (Serpinb 13Ko). By genotyping, we are at the 3rd generation (F3) of Serpinb13ko mice as of today. Since their generation, we have been maintaining the colony, therefore the specific characterization of these mutant mice is entirely unexplored. The serpin B13 is expressed in the skin, a natural inhibitor of cathepsin L, therefore we do expect a skin phenotype. As it is also found in other tissues, we need to fully characterize the physical and physiologic parameters of this mutant strain at different stages of life (and sex). We will perform this with serial, non-invasive ultrasonography (UNM HSC LAR). This presents an exceptional tool to explore lysosomal physiology (hence, relevance to our UNM AIM center and collaborations), with tissues available to explore how this lysosomal mechanism contributes to diseases.
Approved as a DMR by Sub-Committee on 7/2/2019.

200902 - "Xenograft leukemia mouse models to test the in vivo efficacy of drag reducing polymers (DRPs) for prevention of leukemia metastasis."
Reviewers: *12, 27, AV*
A motion for approval was made and carried.
Summary: The leukemias are blood cell cancers with dysregulated growth and malfunction of blood cells. Patients are diagnosed by detecting abnormal blood cells in the bone marrow and receive chemotherapy and irradiation as a standard treatment. Although the cure rate has been improved, drug-resistant cells often appear after treatment and cause a lethal relapse. To extend the cancer-free period after the initial standard treatment, additional preventive therapies against metastasis are required. Since cancer cells need to attach and adhere to blood or lymph vessels to exit from the flow and metastasize into next sites of a body, blocking the process is another new option to target as novel therapies. The critical step to metastasize is shared by most of cancer types, which is initiated with the successful attachment to blood vessels under the blood flow (*ref: attached image*). Several physics conditions such as the flow rate, diameter of vessels and blood viscosity, etc., can affect the process. We have studied the effect of non-toxic blood-soluble reagents onto brain ischemic recovery by modifying the rheological condition of the blood. Based on the reports showing such rheological condition can affect the rate of cancer metastasis, we aim to test its potential benefit to prevent leukemia blast metastasis.
In this study, we are planning to evaluate the preventive effect of non-toxic blood-soluble chemical agents against leukemia metastasis in live animals, which is the only way at present to perform preclinical studies.
Recommended for approval on 6/27/2019.
Discussion during the meeting: The secondary reviewer gave a summary of the protocol. All of the numerous review comments had been addressed during the pre-review. There were no other issues and the protocol was recommended for approval.
Decision: Approved: Yes=10 No=0 Abstained=0 Recused=0

200914 3-yr RW (change in PI) - "BBHI-Preclinical MRI/PET Core for method development, instrument quality control, and diagnostic procedure protocol."
Reviewer: *20, 24, AV*
A motion for DMR was made and carried.

Summary: This protocol is our core protocol to conduct positron emission tomography (PET) scan and magnetic resonance imaging (MRI) scans on mice and rats. We currently have been approved to conduct MRI/PET on mice with ovarian tumors that have been found in the abdominal cavity. Conducting PET scans on these mice will enable a development of novel therapies and diagnostic methodologies, or procedures, for ovarian cancer based on a better understanding of the immune response to ovarian cancer. Upon completion of the PET scan, the mice will then immediately be euthanized. We also were approved to conduct MRI/PET on mice with tau. Tau is a protein in the brain, that builds up and when it does it can cause tangles in the areas of the brain which are important for memory. Additionally, we aim to use mice and rats in the MRI/PET imager to develop more efficient programming sequences (methods) with the MRI and PET that will ensure the optimal contrast is obtained when investigators use the facility. This will benefit both the investigators and the animals by reducing the time and effort needed to get good images using the MRI/PET. Method development will be performed no more than twice per week. It is essential that we use live animals for MRI/PET scans because it provides a quantitative measure of the 3-dimensional distribution of a radiopharmaceutical administered to a live subject noninvasively. The small structures of small animals require a scanner with high spatial resolution. We need to use live animals for MRI/PET in order to monitor progression live as it is happening in the body, and PET and MRI will allow us to do this.

Returned for modification on 7/1/2019.

Discussion during the meeting: The PI responses had not yet been received but this protocol expires before the next convened meeting so it was sent for review by a DMR sub-committee. The reviewers will remain the same per the Chair. There were some questions and issues that were raised that should be considered during the DMR review. What is the funding source and will the new PI take over the existing radiation safety protocol for this study? Species needs to be added to title. The reviewers will remain the same per the Chair.

Decision: Approved for DMR: Yes=10 No=0 Abstained=0 Recused=0

200931 - "Nanoparticle Delivery of Cas9 Editing Machinery." Reviewers: *11, 25, AV*

A motion for approval was made and carried.

Summary: Engineered nanomaterials are being incorporated into many everyday products, including the medicines we take regularly. We are working with investigators at Sandia National Labs to determine whether nanoparticles, specifically mesoporous silica nanoparticle-supported lipid bilayers (protocells), can be used to improve the prevention and treatment of infectious diseases. In particular, we want to know whether protocells can deliver CRISPR-Cas9 gene editing machinery into the lungs or specific cells in the lungs and whether they are better than existing delivery vehicles; we chose CRISPR-Cas9 as the cargo because editing genes essential for infection and dissemination is a potential way alter the course of infection. Since these studies are designed to evaluate feasibility, we decided to use the Ai9 transgenic mouse which carries a transgene that will produce a recombinant fluorescent protein only if the gene was edited by the Cas9 enzyme. We will administer the protcells directly into the lungs (oropharyngeal route) or other routes, and then evaluate the ability of the protocells to deliver CRISPR-Cas9 and guide RNA based on the number and the type of cells in the lungs that are fluorescent. This will be repeated to evaluate additional protocell formulations developed by Sandia National Labs to improve cargo delivery.

Recommended for approval on 7/8/2019.

Discussion during the meeting: The secondary reviewer gave a summary of the protocol. All of the numerous review comments had been addressed during the pre-review. The lay summary had been rewritten and the animal model was added to the title. ABSL 1 is listed in the hazards section but it should be listed as ABSL 2 since they will follow these practices in the ABSL 2 facility. That can be edited administratively. Species needs to be added to title. There were no other issues and the protocol was recommended for approval.
Decision: Approved: Yes=10 No=0 Abstained=0 Recused=0

Item # 5 Major Amendments:

200704 DMR - "Cellular and Molecular Mechanisms of Mild Traumatic Brain Injuries."
Reviewers: *20, 23, AV*
Summary: The original protocol was written for a pilot project and now that the project has been fully funded by the Center for Brain Recovery and Repair. The number of animals will significantly change because this protocol will encompass all the experiments needed for the full proposal. In addition, procedures will also need to be added and modified to include all the proposed studies for the entire proposal. The risk for pain or distress will not increase and in some cases be reduced due to our preliminary studies done with the current protocol.
Approved as a DMR by Sub-Committee on 6/26/2019. Species needs to be added to title.

200769 - "Study of T cell responses in a mouse model of influenza infection."
Reviewers: *17, 23, AV*
A motion for approval was made and carried.
Summary: We are requesting an amendment to treat influenza-infected animals with specific inhibitors of metabolic function that we hypothesize will change the immune response against influenza. Metabolic function of T cells and other immune cells has been of significant interest, and many studies have shown that changing metabolic function can change the outcome of an immune response in autoimmunity and immunotherapy against cancer. However, less is known about whether perturbing metabolism of immune cells might affect immune response against infectious disease. We want to test how 4 compounds that are known to perturb metabolic function of T cells can change T cell response against influenza infection. All of these compounds changes the ability of T cells to generate ATP. Each of these compounds has been used in animal models with no toxic effects or reported organ damage.
We will increase animal numbers by 360 because we will treat 5 animals and use 5 animals as controls. We will repeat the experiment at least 3 times. We will use one set of animals to assess weight loss, then another set of animals to assess viral load and use for imaging. We need to assess viral load and image T cell function in tissues at days 4, 6, 8, 10, 30, and 60 post infection in order to determine whether changing metabolic function also changes the overall outcome throughout the course of infection including during the memory phase of the response.
Recommended for approval on 7/1/2019.
Discussion during the meeting: The primary reviewer was absent so the Chair gave a summary of the protocol. All of the numerous review comments had been addressed during the pre-review. The alternative searches had been updated. Special husbandry was checked because of a special diet for the animals. An SDS should be attached for the agents in use. There were no other issues and the protocol was recommended for approval.
Decision: Approved: Yes=10 No=0 Abstained=0 Recused=0

200789 - "Type 2 Immune Response, Thermogenesis and energy homeostasis."
Reviewers: *22, 26, AV*
A motion for DMR was made and carried.
Summary: Our previous study has found that fibrosis markers were significantly decreased in JunB liver-specific KO hepatocytes. Thus, JunB liver-specific knockout mice and JunB floxed mice as control mice will be used to determine the role of hepatic JunB in the CCl_4-induced liver fibrosis.
Returned for modification on 7/2/2019.
Discussion during the meeting: The PI responses had not yet been received so this protocol was sent for review by a DMR sub-committee. Biosafety approval will be needed before the PI can work with recombinant agents. Species needs to be added to title. The reviewers will remain the same per the Chair.
Decision: Approved for DMR: Yes=10 No=0 Abstained=0 Recused=0

200870 - "Assessment of the immune responses in mice induced by VLP-based vaccines targeting self and foreign antigens."
Reviewers: *12, 27, AV*
A motion for approval was made and carried.
Summary: Rabbits are a widely used model to study atherosclerosis. Their lipid profile and metabolism better represents humans and they are highly sensitive to increases in cholesterol following a high cholesterol diet. We are adding a small rabbit study to this protocol in order to test if PCSK9-VLPs can lower cholesterol in rabbits fed a high-cholesterol diet (HCD). These experiments will also allow us to investigate whether PCSK9-VLPs can inhibit the development of atherosclerosis. At the end of the study, rabbits will be sacrificed and the presence of atherosclerotic lesions will be examined by immunohistochemical analysis. This is a small pilot study in which we propose using no more than 10 rabbits (5 per group).
Sent for Pre-Review 2 on 7/9/2019.
Discussion during the meeting: The secondary reviewer gave a summary of the protocol. The PI should list the acclimation period for rabbits. A minimum of 7 days acclimation is required. This can be done via email. Species needs to be added to title. There were no other issues and the protocol was recommended for approval.
Decision: Approved: Yes=10 No=0 Abstained=0 Recused=0

Item # 6 Minor Amendments:

200658 - "Trafficking of nanoparticles and synthetic RBC in murine breast and ovarian tumors."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/26/2019.

200663 Breeding - "Mouse models for studying the molecular mechanisms of gliogenesis and gliomagenesis."
Reviewer: *AV*
Summary: Add/remove staff.
Administratively approved per Attending Vet on 6/4/2019.

200663 #2 Breeding- "Mouse models for studying the molecular mechanisms of gliogenesis and gliomagenesis."
Reviewers: *AV*
Summary: Species: Mouse; Number of additional animals: 312. I recently received some mice with Nf;p53-Floxe alleles from UTSW to complete a study. I want to maintain these mice until the study is completed.
Approved by Attending Vet on 6/7/2019.

200678 - "Mouse Model for Glial and Glioma Development - Tamoxifen Administration & Electroporation."
Reviewers: *Chair, AV*
Summary: Mouse, 118 additional animals: We recently received Nf1;p53-Flox (Strain J) and Ascl1;Nf1;p53-Flox (Strain K) mice to complete a study. We are requesting 60 experimental animals for Strain J & K, and 58 B6/ICR mice (which will be purchased when needed).
Approved by IACUC Chair and Attending Vet on 6/11/2019.

200694 - "Microvascular dysfunction during hypercholesterolemia"
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/12/2019.

200761 - "Neuroinflammation and Tauopathies; The role of Neuroinflammation in Mouse Model of Tauopathy."
Reviewers: *Chair, AV*
Summary: P301S Stock Number (008169). Increase of 48 animals.
Our previous work with pT181-Qß VLP based vaccine has shown treatment with the vaccine is sufficient to induce a robust and long-lived anti-pT181 (against pathological Tau) antibody response in the sera and the brains of both Non-Tg and rTg4510 mice. We are now looking into a different mouse model; the P301s mouse. This mouse shows a more severe phenotype with an ealrier onset of pathology. This mouse strain is ideal for a closer look at the mechanism of antibody response and clearance of pathological Tau.
Approved by IACUC Chair and Attending Vet on 6/13/2019.

200761 #2 - "Neuroinflammation and Tauopathies; The role of Neuroinflammation in Mouse Model of Tauopathy."
Reviewers: *12 (VC), AV*
Summary: Added glucose monitoring to experimental procedures. Added special husbandry for diet restrictions for fasting glucose testing.
Approved by Vice Chair and Attending Vet on 6/24/2019.

200771 - "Assessment of the immune responses induced by VLP-based vaccines against infectious diseases in mice."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/21/2019.

200794 "Effect of tissue pO2 on free-radical damage in rat and mouse model of ischemic stroke."
Reviewers: *Chair, AV*
Summary: Added new location, PHB88.
Approved by IACUC Chair and Attending Vet on 6/13/2019.

200802 - "Alcohol and developing neuronal circuits: characterization using mice."
Reviewers: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/13/2019.

200823 - "Murine Models to study the impact of the peritoneal immune environment on ovarian cancer progression and response to treatment - COMBINED PROTOCOL."
Reviewers: *Chair, AV*
Summary: There will be no increase in pain or distress and no increase in animal numbers. We are adding MRI/PET imaging to our vaccine study in addition to existing IVIS imaging to determine if non-invasive imaging can be used to track therapeutic efficacy.
Approved by IACUC Chair and Attending Vet on 6/7/2019.

200843 - "Molecular Regulators of T-Acute Lymphoblastic Leukemia (T-ALL) cell migration."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/11/2019.

200848 - "Mechanisms of hypoxic pulmonary hypertension in a mouse model."
Reviewer: *12 (VC)*
Summary: Add/remove staff.
Administratively approved per IACUC Vice Chair on 6/4/2019.

200848 #2 - "Mechanisms of hypoxic pulmonary hypertension in a mouse model."
Reviewers: *12 (VC), AV*
Summary: We need to add 2 strains of mice to use as recipient mice in the Tv-DTH assays. We are having inconsistent results when using C57B6/J and our collaborators in Madison, WI mainly use CB17 SCID mice. Dr. Judy Cannon has NSG mice which are similar. We would like to compare the Tv-DTH responses that we get in C57B6/J with NSG and CB17 SCID mice. We do not need to add more mice to the protocol.
Approved by Vice Chair and Attending Vet on 6/18/2019.

200860 - "Metabolic Phenotype of the Cerebral Vascular Wall in a Rat Model of Hypertension."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/12/2019.

200889 - "Mechanisms of Vascular Toxicity from Inhaled Toxicants in Pregnant Rodents."
Reviewer: *Chair*

Species: Mouse, Rat
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 6/11/2019.

200907 - "Investigating how different tungsten routes of exposure affect breast cancer progression in Mice."
Reviewers: *12 (VC)*
Administratively approved per Vice Chair on 6/20/2019.

Item # 7 Annual Renewals:

200606 - "Tissue Protocol for Spreading Depolarization in Peripheral Tissues."
Reviewer: *12 (VC), AV*
Approved by Vice Chair and Attending Vet on 7/3/2019.

200641 DMR - "A mouse model to study inflammatory diseases."
Reviewer: *Chair*
Approved by IACUC Chair on 6/7/2019.

200643 - "Simultaneous determination of novel blood biomarkers of hypoxia exposure and cardiovascular parameters in conscious rats. "
Reviewer: *12 (VC)*
Approved as a DMR by IACUC Vice Chair on 6/5/2019.

200710 - "Nasal Administration of Epinephrine/Phentolamine in a Rat Model - A Proof of Concept Study."
Reviewer: *12 (VC)*
Sent for Vice Chair Review on 6/26/2019.

200723 DMR - "Imaging of the immune response in a murine ovarian cancer model after checkpoint inhibition."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 6/13/2019.

200725 Closure - "Production of antibodies against *Staphylococcus aureus* autoinducing peptides in rabbit."
Reviewer: *Chair*
Summary: The antibodies produced by vaccinated mice did not recognize the target antigen.
Closed administratively per IACUC Chair on 5/31/2019.

200728 Breeding - "Rodent models of pulmonary hypertension, intermittent hypoxia induced systemic hypertension and asthma."
Reviewer: *AV*
Approved as a DMR by Attending Vet on 6/5/2019.

General Business:

1) IACUC Concerns –
   a. SOPs – There was a discussion about how the IACUC should review SOPs, which ones should be reviewed, and how often they should be reviewed, etc. There is a draft SOP for how to review and approve SOPs. The OACC will share a list of IACUC SOPs and some draft SOPs with the committee via email.
   b. Fume Hood in G65B – Not all of the fume hoods are currently certified. CSCAN is still on site certifying hoods. SRS stated that use of fume hoods can continue for those hoods with certifications that expired in May as long as there is air flow and there are no known problems or issues.

The meeting was adjourned at 1:18 PM.
Respectfully submitted by the Recording Secretary_____

HSC IACUC Meeting Minutes for Thursday, August 1, 2019
Meeting Place – [redacted]
Meeting time - 12:16 pm – 1:08 pm

Members Present
Attending Veterinarian
Chair
IACUC Administrator (NV)
Member #8
Member #11
Member #12 (Vice-Chair)
Member #20
Member #22
Member #25
Member #26
OACC Operations Manager, Recording Secretary (NV)
SRS Rep (NV)

Members Absent
ARF Representative (NV)
BHC Representative (NV)
EOHS Representative (NV)
Member #17
Member #18
Member #23
Member #24
Member #27
Radiation Safety Representative (NV)

NV= non-voting members, consultant or staff

Per the request of the Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 9

Guests: SRS Rep and HSLIC Research Librarian who are future committee members.

Item # 1: Approval of Agenda:
A motion for approval of the August 1, 2019 agenda was made and carried. The agenda was approved as presented.
Decision: Approved: Yes=9 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes:
A motion for approval of the July 11, 2019 meeting minutes was made and carried. Some identifiers and an extraneous words were removed from pages 6 and 10 and in general business. A name was removed on page 11. The minutes were approved as amended.
Decision: Approved: Yes=9 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200423 Major DMR – "Study of papillomavirus entry and infection in mouse models."
Reviewers: *17, 25, AV*
Summary: We would like to (1) test a potential prophylactic agent (FDA approved in humans), (2) include another means of tissue wounding (at a different tissue site) for analysis of papillomavirus infections, (3) test sex hormone effects in PV infections. Additional numbers of mice will be needed to carry out this work.
Sent for DMR #2 on 6/26/2019. Waiting for updated animal numbers table.

200710 Annual- "Nasal Administration of Epinephrine/Phentolamine in a Rat Model - A Proof of Concept Study."
Reviewer: *Chair*
Species: Rat
Approved by IACUC Chair on 7/17/2019.

200789 Major DMR- "Type 2 Immune Response, Thermogenesis and energy homeostasis
Reviewers: *22, 26, AV*
Summary: Our previous study has found that fibrosis markers were significantly decreased in JunB liver-specific KO hepatocytes. Thus, JunB liver-sepecific knockout mice and JunB floxed mice as control mice will be used to determine the role of hepatic JunB in the CCl_4-induced liver fibrosis.
Approved as a DMR by Sub-Committee on 7/18/2019.

200914 3-yr RW (change in PI) DMR - "BBHI-Preclinical MRI/PET Core for method development, instrument quality control, and diagnostic procedure protocol."
Reviewer: *20, 24, AV*
Summary: This protocol is our core protocol to conduct positron emission tomography (PET) scan and magnetic resonance imaging (MRI) scans on mice and rats. We currently have been approved to conduct MRI/PET on mice with ovarian tumors that have been found in the abdominal cavity. Conducting PET scans on these mice will enable a development of novel therapies and diagnostic methodologies, or procedures, for ovarian cancer based on a better understanding of the immune response to ovarian cancer. Upon completion of the PET scan, the mice will then immediately be euthanized. We also were approved to conduct MRI/PET on mice with tau. Tau is a protein in the brain, that builds up and when it does it can cause tangles in the areas of the brain which are important for memory. Additionally, we aim to use mice and rats in the MRI/PET imager to develop more efficient programming sequences (methods) with the MRI and PET that will ensure the optimal contrast is obtained when investigators use the facility. This will benefit both the investigators and the animals by reducing the time and effort needed to get good images using the MRI/PET. Method development will be performed no more than twice per week. It is essential that we use live animals for MRI/PET scans because it provides a quantitative measure of the 3-dimensional distribution of a radiopharmaceutical administered to a live subject noninvasively. The small structures of small animals require a scanner with high

spatial resolution. We need to use live animals for MRI/PET in order to monitor progression live as it is happening in the body, and PET and MRI will allow us to do this.
Approved as a DMR by Sub-Committee on 7/19/2019.

Item # 4 New Protocols:

200605 3-yr RW - "Time Course of Injury Mechanisms in a Rat Model of Acute Ischemic Stroke."
Reviewers: *12, 27, AV*
A motion for DMR was made and carried.
Summary: Presently, patients suffering stroke have only one treatment available, which is to open the clot in the blood vessel with the use of an enzyme tissue plasminogen activation (tPA) which has to be administered in less than 3 hrs after the stroke. Of the approximately 750,000 acute strokes per year in the US, about 30% of which are ischemic strokes, only 5% are treated with tPA for various reasons. An ischemic stroke develops when a blood vessel, supplying blood to an area of the brain, becomes blocked by a blood clot. The primary reason is that the time since the stroke started is unknown or the patients arrive beyond the 3 hr time window for the use of drugs to break up the blood clot (thrombolytic therapy). The fact that there is only one treatment for acute ischemic stroke despite the many drug and therapy trials conducted in patients and the hundreds of drugs shown effective in animals raises the question as to why this is the case. Where is the disconnect between the success of therapies in animals and the lack of translation to patients?
This problem is likely multifactorial. However, we identified two major reasons for this disconnect between animal and patient treatments for acute stroke. First, the animal models are by design, very reproducible whereas the strokes in patients are widely varying from very small strokes with little benefit from therapy and large devastating strokes that nothing would be able to improve outcome. Second, inherent in the concept of therapy for acute stroke is the notion that there is salvageable tissue that can be rescued by therapeutic intervention. The tissue that can be salvaged is known as the "Penumbra" which is generally thought of as the area surrounding the core or irreversibly damaged tissue as in an egg yolk surrounded by the white of the egg. However, the penumbra does not always occur this way. In 70% of the cases, the penumbra occurs as archipelagos within the core which complicates estimation of the volume of the penumbra or salvageable tissue. Differentiation of the penumbra volume from the core tissue volume cannot be done clinically due to the limitations of the clinical computer MRI or CT software. Thus, clinicians cannot determine the precise penumbra volume and this limitation in the clinical estimation of penumbra volume before therapeutic intervention in acute stroke in patients.
Sent for Pre-Review 1 on 7/23/2019.
Discussion during the meeting: One set of review comments is still needed so this protocol submission was sent immediately for DMR. Per the Chair, the reviewers will remain the same.
Decision: Approved: Yes=9 No=0 Abstained=0 Recused=0

200922 3-yr RW – "Murine models of neoplastic development and therapeutics."
Reviewers: *18, 8, AV*
A motion for approval was made and carried.
Summary: Project 1: A new strategy that is being developed for HIV/AIDS prevention is the use of topical antiviral drugs. These have been tested in large clinical trials in the form of topical

intravaginal or intrarectal gels for high-risk populations. There is concern about this approach because some of these drugs activate oncogenes. The results of our studies indicate that mice harboring human papilloma virus (HPV) genes are more likely to develop cervical cancers. We want to confirm these findings and we aim to better understand the mechanism of oncogenesis by antiviral drugs. In particular we are interested in the activation of cell cycle genes and non-coding RNAs as we already have mouse models showing that these pathways are highly synergistic for tumor formation in mouse models. We will treat transgenic mice, that carry human papilloma virus oncogenes, with topical microbicides to see how the pattern of gene expression is altered and whether this corresponds to prior human studies.
Project 2: A common aspect of almost all tumors is the activation cell cycle gene pathways that causes continuous cell growth. We discovered a gene (Xpcl1) that produces combination of microRNAs. Although they do not encode proteins themselves, microRNAs prevent expression of other genes. We have shown that too much Xpcl1 impairs normal T-lymphocyte development, and also can causes lymphomas. Further, the combination of Xpcl1 overexpression and loss of a cell cycle inhibitor gene (called p27) is highly synergistic, but we do not yet know why. We also do not know what genes are being targeted by the Xpcl1 microRNA. We would like to better understand how the microRNA cause tumors, how they interact with cell cycle genes, and whether they might serve as predictors for human tumors. We have created novel transgenic and targeted mouse gene mutations that will allow us to find the downstream targets of Xpcl1. We will harvest tissues from these animals for biochemical assays and flow cytometry.
Project 3: Building on our studies of mice with targeted mutations of p27 and Xpcl1, we recently identified these same biochemical pathways as being predictors of poor outcome in both human AML (acute myeloid leukemia) and human ALL (acute lymphoid leukemia). We are using human tumors xenografted into mice (PDX models) to determine whether the gene expression and mutation profiles will predict responsiveness to targeted therapies. This will be done both in a screening assays in vitro, and in a drug sensitivity study in PDX mice.
Sent for Pre-Review 1 on 7/11/2019.
Discussion during the meeting: The AV gave a summary of the protocol submission. This protocol only has minor items that still need to be resolved so it was sent for DMR. Per the Chair, the reviewers will remain the same.
Decision: Approved: Yes=9 No=0 Abstained=0 Recused=0

200923 3-yr RW DMR by Vet - "Lab Mouse Breeding Colony."
Reviewer: *AV*
Summary: This project will be responsible for the breeding of lab mice to be used for experimental projects investigating new pathways for cancer therapeutics.
Approved as a DMR by Attending Vet on 7/24/2019.

200933 3-yr RW - "Post-transcriptional control of neuronal mRNAs in normal conditions and mouse models of psychiatric illnesses/addiction."
Reviewers: *17, 23, AV*
A motion for approval was made and carried.
Summary: Our laboratory is interested in understanding mechanisms of abnormal brain development and function using mouse models of disease. Our goal is to provide better insights into the consequences of abnormal brain development caused by genetic illnesses such as schizophrenia and autism as well as exposure to drug of abuse such as cocaine. To this end, we

use different genetic mouse lines that display increased preference for cocaine, have higher reinstatement of a food reward, or have learning and memory deficits. In addition, in other studies, we expose adult mice to cocaine and changes in analyze gene expression. By understanding the basic mechanisms underlying these disorders, we hope to contribute to the development of better diagnosis and treatment strategies.
Recommended for approval on 7/30/2019.
Discussion during the meeting: The Chair gave a summary of the protocol submission. This is a 3-yr Rewrite where not much has changed and all of the review comments had been addressed during the pre-review so the protocol was recommended for approval.
Decision: Approved: Yes=8 No=0 Abstained=0 Recused=1

200944 Breeding DMR by Vet - "Mechanisms of Vascular Toxicity from Inhaled Toxicants in Pregnant Rodents."
Reviewer: *AV*
Summary: Air pollution exposure during pregnancy is associated with adverse health effects to both the mother and child. In the present study, we propose to examine the linkages between inhaled pollutant exposure and how the mother may be vulnerable to pregnancy-related high blood pressure and heart failure. These studies will help us 1) confirm that there is a causal relationship between exposure and hypertension and 2) identify biological markers of exposure that may be valuable in confirming these studies in humans.
Approved as a DMR by Attending Vet on 7/31/2019.

200945 - "Role of TRPV4 in obesity-induced vascular dysfunction in mice."
Reviewers: *11, 25, AV*
Summary: Lean and obese mice will be used to evaluate causes of artery disease in obesity. Specifically, the studies will determine if obesity causes changes in the cells that line arteries so that they no longer produce hydrogen sulfide. The production of hydrogen sulfide by the cells that line arteries is important for normal function of arteries and to prevent blood clots and plaques from developing in arteries. We hypothesize that the increased body fat leads to changes in the cell membranes so that hydrogen sulfide is not made leading to decreased diameter of the arteries and decreased responsiveness of the arteries to signals that normally open up the arteries. We will look at the production of hydrogen sulfide in small arteries from mice that are lean or obese and at the responses of small arteries from lean and obese mice to applied hydrogen sulfide. Finally, we will look at one potential target of hydrogen sulfide in the cells to see if it has a loss of function in the obese mice compared to its function in the arteries from the lean mice.
Recommended for approval on 7/24/2019. ***We could not vote on this protocol because two members needed to recuse themselves so it will be sent for Approval for DMR after the convened meeting.***

200949 - "Preserving the Ischemic Penumbra with a Drag Reducing Polymer."
Reviewers: *20, 24, AV*
A motion for approval was made and carried.
Summary: In studies on anesthetized Sprague Dawley rats subjected to a stroke in the brain, we will determine whether a drug we have patented for the treatment of low blood flow in the brain will preserve and expand the ischemic penumbra which is tissue that is at risk because of low

blood flow, but not yet dead, which would greatly increase the chances of effective therapeutic intervention and recovery. Studies testing neuroprotection in stroke have all failed in clinical trials because it was not until recently (2008) and later that it was realized that the patients suffering a stroke had to have a so-called ischemic penumbra (tissue under threat of dying but not yet dead) in order to show benefit with intra-arterial thrombectomy (IAT) where the clot is pulled out of the brain with a catheter. If the clot in the large vessel is retracted in time, the patient may suffer no brain damage. If successful in prolonging the duration of the ischemic penumbra or even increasing the size of the ischemic penumbra the patients are likely to benefit from either thrombolysis where an enzyme is injected to dissolve the clot or thrombectomy where the clot is pulled out.

Returned for modification on 7/31/2019.

Discussion during the meeting: PI responses are needed so this protocol submission was sent for DMR. Per the Chair, the reviewers will remain the same.

Decision: Approved: Yes=9 No=0 Abstained=0 Recused=0

Item # 5 Major Amendments:

200592 - "The role of the estrogen receptor GPER/GPR30 in reproduction and carcinogenesis."
Reviewers: *22, 26, AV*
A motion for approval was made and carried.
Summary: This amendment is to add procedures already approved on protocol #16-200579 to this protocol, #16-200592, in anticipation of closing 16-200579. These studies are closely related to the overall goals of the experiments covered under 16-200579.
We propose to examine the role of GPER in T cells in colon tumor growth. Thus, we will utilize Rag2 KO mice on the B6 background with our MC38 syngeneic flank injection model. We will inject up to 10 million WT, GPER KO, or G-CSF KO CD4 T cells into B6 mice at least 24 hours before flank injection of 2 million MC38 cells. T cells will be isolated from the spleens of WT, GPER KO, and G-CSFR KO B6 mice by negative selection using magnetic bead kits. T cells will be sex matched to injection mice. Tumor growth will be monitored and mice euthanized up to 24 days after tumor injection. 10/group, males and females of WT and GPER KO T cells for a total of 30 mice.
We would also like to examine the role of GPER and G-CSFR KO macrophages in tumor growth. In an approach we have used for the MK2 project, we propose to add 1 million bone marrow derived macrophages into the tumor microenvironment 24 hours after MC38 tumor cell injection, and once a week for two weeks. Macrophages will be sex matched to injection mice. Tumor growth will be monitored and mice euthanized up to 24 days after tumor injection. 10/group, males and females of WT and GPER KO macrophages for a total of 30 mice.
Total mice for 6/28/19 amendment: 60.

Recommended for approval on 7/9/2019.

Discussion during the meeting: The primary reviewer gave a summary of the protocol submission. The PI should add the species to the title which can be done via email. All of the review comments had been addressed during the pre-review so the protocol amendment was recommended for approval.

Decision: Approved: Yes=9 No=0 Abstained=0 Recused=0

Item # 6 Minor Amendments:

200470 - "Training Protocol for Brain Recovery and Repair Preclinical Core."
Reviewers: *Chair*
Species: Mouse
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 7/31/2019.

200613 - "Mouse and Rat Models of Orofacial Nerve Injury, Back Pain and Visceral Pain for Preclinical Studies of Pain Mechanisms and Potential Therapeutics".
Reviewers: Chair, AV
Summary: We are requesting approval to add one additional experimental non-opioid therapeutic for testing in our previously approved mouse model of chronic orofacial pain: BPY-104. Testing this cellular stress inhibitor will provide better understanding of cellular stress and autophagy occurring during persisting pain potentially related to the neuronal circuitry alterations occurring in these limbic cortical regions during the chronification of pain.
We will not be requesting any additional animals; we will repurpose numbers from initially proposed experiments that were not performed due to changes in research objectives. We will not be requesting any changes to the previously approved models that would increase pain or distress to the animals. It is our hope that these drugs will prove to be therapeutic and relieve pain.
Sent for Chair and Vet Review 1 on 7/26/19.

200641 - "A mouse model to study inflammatory diseases."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 7/15/2019.

200717 - "A mouse model of Mycobacterium abscessus lung infection that mimics human infection."
Reviewers: *Chair, AV*
Summary: In our experimental Cre+ mice, cre recombinase is linked to a tamoxifen promoter and the floxed gene *IFT88* (gene product necessary for normal cilia function) is deleted. The Cre+ mice who have been treated with tamoxifen are gaining weight relative to the control Cre- mice who received tamoxifen. There has been recent research on the role of ciliopathies in obesity. Mouse studies have found that hypothalamic neurons express cilia that are involved in appetite control. Targeted knock out of several genes involved in cilia function specifically in neurons (including *IFT88*) results in hyperphagia. This is an appetite-related phenomenon and not metabolic derangement. Therefore, there is a need to limit food intake in the mice to maintain body weight in the range for normal C57BL/6J mice (the background strain).
Approved by IACUC Chair and Attending Vet on 7/24/2019.

200769 - "Study of T cell responses in a mouse model of influenza infection."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 7/24/2019.

200806 Breeding - "Mouse Models of Obesity and Diabetes."
Reviewer: *AV*
Summary: We are going to generate PDGFRa-CRE JUNB KO by cross JUNB flox(n=3) mice with PDGFRa-CRE(n=1)(from Jackson lab).
Approved by Attending Vet on 7/16/2019.

200823 - "Murine Models to study the impact of the peritoneal immune environment on ovarian cancer progression and response to treatment - COMBINED PROTOCOL."
Reviewer: *Chair*
Summary: Add/remove staff.
Administratively approved per IACUC Chair on 7/16/2019.

200884 - "Breeding protocol for ovarian cancer mouse models."
Reviewer: *AV*
Summary: Add/remove staff.
Administratively approved per Attending Vet on 7/16/2019.

Item # 7 Annual Renewals:

200628 Closure - "Refinement of the Fischer 344 rat model of pneumonic tularemia. "
Reviewer: *Chair*
Summary: This project ended in December and there is no more funding.
Closed administratively per IACUC Chair on 7/16/2019.

200653 DMR w/ Minor – "A Mouse Model for Mechanisms of Immune Dysregulation Produced by Uranium, Arsenic, and Metal Mixtures (Biomedical Project (BP2), Superfund Center)."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved as a DMR by IACUC Chair on 7/9/2019.

200730 DMR - "Breeding protocol for a mouse model of *Mycobacterium abscessus* lung infection using mice with abnormal lung airways."
Reviewer: *AV*
Approved as a DMR by Attending Vet on 7/9/2019.

General Business:

1) IACUC Concerns – HSC IACUC Semi-annual inspections will take place in September.

The meeting was adjourned at 1:08 PM.
Respectfully submitted by the Recording Secretary_____

HSC IACUC Meeting Minutes for Thursday, September 5, 2019
Meeting Place – [redacted]
Meeting time - 12:11 pm – 1:32 pm

Members Present
Attending Veterinarian
BHC Representative (NV)
EOHS Representative (NV)
IACUC Administrator (NV)
Member #8
Member #11
Member #12 (Vice-Chair)
Member #20
Member #22
Member #23
Member #24
Member #26
Member #27
Member #28 (Research Librarian)
OACC Operations Manager, Recording Secretary (NV)

Members Absent
ARF Representative (NV)
Chair
Member #17
Member #18
Member #25
Radiation Safety Representative (NV)
SRS Rep (NV)

NV= non-voting members, consultant or staff

Per the request of the Vice-Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 11

Item # 1: Approval of Agenda:
A motion for approval of the September 5, 2019 agenda was made and carried. The agenda was approved as presented.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes:
A motion for approval of the August 1, 2019 meeting minutes was made and carried. Some identifiers were removed from page 1. The minutes were approved as amended.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200423 Major DMR – "Study of papillomavirus entry and infection in mouse models."
Reviewers: *17, 25, AV*
Summary: We would like to (1) test a potential prophylactic agent (FDA approved in humans), (2) include another means of tissue wounding (at a different tissue site) for analysis of papillomavirus infections, (3) test sex hormone effects in PV infections. Additional numbers of mice will be needed to carry out this work.
Approved as a DMR by Sub-committee on 8/9/19.

200605 3-yr RW DMR - "Time Course of Injury Mechanisms in a Rat Model of Acute Ischemic Stroke."
Reviewers: *12, 27, AV*
Summary: Presently, patients suffering stroke have only one treatment available, which is to open the clot in the blood vessel with the use of an enzyme tissue plasminogen activation (tPA) which has to be administered in less than 3 hrs after the stroke. Of the approximately 750,000 acute strokes per year in the US, about 30% of which are ischemic strokes, only 5% are treated with tPA for various reasons. An ischemic stroke develops when a blood vessel, supplying blood to an area of the brain, becomes blocked by a blood clot. The primary reason is that the time since the stroke started is unknown or the patients arrive beyond the 3 hr time window for the use of drugs to break up the blood clot (thrombolytic therapy). The fact that there is only one treatment for acute ischemic stroke despite the many drug and therapy trials conducted in patients and the hundreds of drugs shown effective in animals raises the question as to why this is the case. Where is the disconnect between the success of therapies in animals and the lack of translation to patients?
This problem is likely multifactorial. However, we identified two major reasons for this disconnect between animal and patient treatments for acute stroke. First, the animal models are by design, very reproducible whereas the strokes in patients are widely varying from very small strokes with little benefit from therapy and large devastating strokes that nothing would be able to improve outcome. Second, inherent in the concept of therapy for acute stroke is the notion that there is salvageable tissue that can be rescued by therapeutic intervention. The tissue that can be salvaged is known as the "Penumbra" which is generally thought of as the area surrounding the core or irreversibly damaged tissue as in an egg yolk surrounded by the white of the egg. However, the penumbra does not always occur this way. In 70% of the cases, the penumbra occurs as archipelagos within the core which complicates estimation of the volume of the penumbra or salvageable tissue. Differentiation of the penumbra volume from the core tissue volume cannot be done clinically due to the limitations of the clinical computer MRI or CT software. Thus, clinicians cannot determine the precise penumbra volume and this limitation in the clinical estimation of penumbra volume before therapeutic intervention in acute stroke in patients.
Returned for modifications on 8/5/2019.

200945 DMR - "Role of TRPV4 in obesity-induced vascular dysfunction in mice."
Reviewers: *11, 25, AV*
Summary: Lean and obese mice will be used to evaluate causes of artery disease in obesity. Specifically, the studies will determine if obesity causes changes in the cells that line arteries so that they no longer produce hydrogen sulfide. The production of hydrogen sulfide by the cells

that line arteries is important for normal function of arteries and to prevent blood clots and plaques from developing in arteries. We hypothesize that the increased body fat leads to changes in the cell membranes so that hydrogen sulfide is not made leading to decreased diameter of the arteries and decreased responsiveness of the arteries to signals that normally open up the arteries. We will look at the production of hydrogen sulfide in small arteries from mice that are lean or obese and at the responses of small arteries from lean and obese mice to applied hydrogen sulfide. Finally, we will look at one potential target of hydrogen sulfide in the cells to see if it has a loss of function in the obese mice compared to its function in the arteries from the lean mice.
Approved as a DMR by Sub-committee on 8/5/2019.

200949 DMR - "Preserving the Ischemic Penumbra with a Drag Reducing Polymer in a Rat Model of Stroke."
Reviewers: *20, 24, AV*
Summary: In studies on anesthetized Sprague Dawley rats subjected to a stroke in the brain, we will determine whether a drug we have patented for the treatment of low blood flow in the brain will preserve and expand the ischemic penumbra which is tissue that is at risk because of low blood flow, but not yet dead, which would greatly increase the chances of effective therapeutic intervention and recovery. Studies testing neuroprotection in stroke have all failed in clinical trials because it was not until recently (2008) and later that it was realized that the patients suffering a stroke had to have a so-called ischemic penumbra (tissue under threat of dying but not yet dead) in order to show benefit with intra-arterial thrombectomy (IAT) where the clot is pulled out of the brain with a catheter. If the clot in the large vessel is retracted in time, the patient may suffer no brain damage. If successful in prolonging the duration of the ischemic penumbra or even increasing the size of the ischemic penumbra the patients are likely to benefit from either thrombolysis where an enzyme is injected to dissolve the clot or thrombectomy where the clot is pulled out.
Returned for modification on 7/31/2019.

Item # 4 New Protocols:

200950 - "Neurovascular Consequences of Inhaled Uranium Minesite-Derived Dusts in Mice."
Reviewers: *17, 26, AV*
A motion for approval was made and carried.
Summary: Poor remediation of abandoned commercial uranium mines throughout the Southwestern United States has subjected Native tribal communities to metal-based (uranium, vanadium, arsenic) environmental exposures. There has also been an association between metal expsosure and autoimmune markers on these tribal lands. Recent data suggest that inhalation of fugitive mine-site derived dust may have neurovascular consequences in both healthy and autoimmune-prone individuals. People living within a few miles of such mine sites may be at risk of inhaling those dusts. To accomplish this, we will use a battery of exposure paradigms including a specially-designed mobile laboratory, contributed by colleagues at Michigan State University (AirCARE1), which houses rodents and permits exposure to dusts in the air around the lab. Mice will be exposed by inhalation to the dusts close to the mine site, and we will then explore the toxicity of these particles to the lungs, vasculature and brain in both wild type and autoimmune-prone mice. These studies will provide important information about health risks of

inhaled dusts for those living near these sites. These data will best serve policymakers in the National Institutes of Health and also the Environmental Protection Agency to make informed decisions relevant to public health. The proposed research intends explore this relationship and evaluate the mechanism underlying mine-site derived PM-induced endothelial dysfunction and long-term neurological consequences in both healthy and autoimmune-prone individuals.
Sent for Pre-Review 3 on 8/27/2019.
Discussion during the meeting: The secondary reviewer gave a summary of the protocol. There was a question about what happens to the animals after imaging. The PI should better describe the rationale for the use of exosomes. The number of doses in the dosing table should match the description of the dosing procedures. There were still a few questions so the protocol was sent for DMR and will be returned for modifications. The motion for approval was withdrawn and a motion for approval for DMR was made and carried. The reviewers will remain the same per the Vice-Chair.
Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200953 3-yr RW - "Mouse Training Protocol for Brain Recovery and Repair Preclinical Core."
Reviewers: *18, 23, AV*
A motion for approval was made and carried.
Summary: It is critical that all personnel working with laboratory animals are trained in applicable methods associated with the species used and techniques required under their respective animal research programs. Assuring competence not only improves animal welfare and scientific integrity but also promotes research compliance. Procedures that will be trained under this protocol include: Basic handling, administration of anesthesia (injectable and inhalation), blood collection, agent dosing (oral, injectable via multiple routes – subcutaneous, intradermal, intraperitoneal, intravenous via tail vein or retro-orbitally, etc.), surgery to include sterile technique, euthanasia, necropsy for tissue collection,
in-vivo electrophysiology (anesthetized and awake behaving animals), in-vivo imaging (anesthetized and awake behaving animals), and a variety of behavioral tasks (open-field, novel object recognition, cylinder task, Y-maze, Zero-maze, Morris water maze, touchscreen based learning and memory tasks, contextual fear conditioning, CatWalk gate analysis). To avoid pain or distress, anesthesia will be administered prior to conduct of potentially painful procedures and euthanasia will be administered after completion of invasive techniques such as surgery without them being allowed to recover from anesthesia, except when survival surgery is the primary training outcome. Laboratory mice are the primary models used in research at the Pre-Clinical Core and training is generally conducted using the target species, unless a viable non-animal model is available. Also, rather than purchasing or breeding animals solely for training, when possible, we will use rodents scheduled for euthanasia that were at end-points from survival research, retired breeders, or inappropriate genotype that are not useful for research.
Sent for Pre-Review 1 on 8/22/2019.
Discussion during the meeting: The PI gave a summary of the protocol. There was a question about the temperature of the water during some of the water tasks used for behavioral testing. There was also a question about the dose for one of the agents. Should tamoxifen be removed from the protocol? The PI is being changed due to changes in the core leadership roles. Add the species to the title. There were still a few questions so the protocol was sent for DMR and will be returned for modifications. The motion for approval was withdrawn and a motion for

approval for DMR was made and carried. The reviewers will remain the same per the Vice-Chair.
Decision: Approval for DMR: Yes=10 No=0 Abstained=0 Recused=1

200955 DMR - "Assessment of pulmonary edema using a breath gas sensor in rats".
Reviewers: *22, 8, AV*
Summary: The project will address an unmet need for early detection of pulmonary edema (water on the lungs), a condition underlying acute respiratory distress syndrome and acute heart failure. Pulmonary edema can be life threatening, but treatments are available if detected early. This project is attempting to develop a non-invasive method to measure biomarkers in the exhaled breath where changes in their levels would indicate pulmonary edema. This project will use rats that will be sacrificed for collection of their heart/lung system that will be used in experiments where we will artificially induce pulmonary edema and measure changes in our biomolecules of interest.
Approved as a DMR by Sub-Committee on 8/15/19.

200956 - "Evaluate the Effect of Microenvironment on Tungsten-enhanced Breast Cancer Metastasis to the Lung using Orthotopic Mammary Cancer Mouse Models."
Reviewers: *11, 25, AV*
A motion for approval was made and carried.
Summary: Tungsten is classified as an emerging environmental toxicant, due to increased human exposure, yet lack of understanding the human health risks. Currently, very little information is known about the role of tungsten exposure in cancer progression. Recently, a cohort of breast cancer patients was accidentally exposed to tungsten from a tungsten-based shield used during intraoperative radiotherapy. Given the limited data investigating the role of tungsten on progression and metastasis, we conducted an animal study using an aggressive breast cancer mouse model, representing late state disease. We found that tungsten drove breast cancer progression by increasing metastasis in the lung. This was associated with an increase in multiple cell types in the microenvironment in the lung metastatic niche and periphery, however what role these cell types play in tungsten-enhance breast cancer metastasis is unknown. In this project we will use a series of inhibition and activation experiments to determine which cell types in the microenvironment are necessary for tungsten-enhanced breast cancer metastasis to the lung. These data will be critical to narrow down which microenvironment cell types should be the focus of more mechanistic tungsten-related cancer grants in the future. This is a novel project because it is the first step to understanding how an environmental agent can target the microenvironment to drive cancer progression, which is an under investigated area of research.
Recommended for approval on 8/29/2019.
Discussion during the meeting: The primary reviewer gave a summary of the protocol. The PI simplified the lay summary. There was a question about early removal criteria that had also been addressed during the pre-review. Add the species to the title. All of the other review comments had been addressed during the pre-review so the protocol was recommended for approval.
Decision: Approved: Yes=11 No=0 Abstained=0 Recused=0

200957 3-yr RW - " Mechanisms of Neuronal Cell Death and Repair in Mouse Models of Neurological Disorders."
Reviewers: *20, 24, AV*

A motion for DMR was made and carried.
Summary: Project 1: Neural Stem Cells in Recovery and Repair Following Stroke. Stroke is a leading cause of long-term disability, with a high percentage of survivors requiring self-care assistance. This proposal is based on the scientific premise that adult neural stem cells (NSCs) contribute to plasticity and repair of the adult mammalian brain, and that enhancement of this regenerative response holds therapeutic promise in promoting long-term recovery of function following stroke. The focus of the current proposal is to elucidate the role of hypoxic signaling as a key regulatory mechanism in NSC function and the mechanisms by which endogenous NSCs promote revascularization and repair. These studies will utilize transgenic mice in which NSCs can be identified and genetically manipulated in a well-characterized model of ischemic stroke.
Project 2: Alcohol and Neurogenesis. Fetal alcohol spectrum disorder represents a significant health problem, with prevalence estimated to be as high as 4.5 per 1,000 live births. Despite this, few empirically supported interventions are available for mitigating the cognitive and behavioral disabilities associated with FASD. This work aims to identify novel therapeutic approaches to reverse learning deficits and hippocampal dysfunction. We are focused on hippocampal neurogenesis as a relevant target. These studies will utilize transgenic mice in which adult-generated neurons can be identified, quantified and electrophysiologically recorded from by fluorescent reporter expression in well-characterized models of prenatal alcohol exposure. In addition, we will determine how prenatal alcohol impacts oligodendrocyte function, including remyelination efficiency.
Project 3: SNAP 25 in network function: Adult neurogenesis is a form of brain plasticity that is important for certain forms of learning and memory. This research will investigate fundamental principles that are required for the proper integration and function of newborn neurons within an existing brain circuitry. It is hoped that this research will reveal fundamental knowledge important for enhancing cognition in aging and neurological disease, and in the context of brain repair. Here we will utilize a unique transgenic mouse in which SNAP-25, a protein required for synaptic transmission, is selectively knocked out of newborn dentate granule neurons in adult mice, thus genetically silencing these cells. This will allow us to figure out the role of these cells in hippocampal network activity under normal non-pathological conditions.
Sent for Pre-Review 1 on 8/21/2019. Expires 9/29/2019.
Discussion during the meeting: This protocol had not yet been returned for modifications so it was sent immediately for DMR. Add the species to the title. The reviewers will remain the same per the Vice-Chair.
Decision: Approved: Yes=11 No=0 Abstained=0 Recused=0

200959 - "Rapid Alcohol Detection and Monitoring in Dermal Interstitial Fluid (ISF) in Rats."
Reviewers: *17, 8, AV*
A motion for DMR was made and carried.
Summary: Excessive alcohol consumption has numerous detrimental effects which can include heart, lung, reproductive, liver, and kidney problems. Alcohol consumption may also increase the likelihood of cancer. In addition to direct health concerns, excessive alcohol use may also develop into alcoholism and is also responsible for thousands of DWI fatalities each year in the United States alone. There is an urgent need for new testing devices that can 1) determine if an individual has consumed any alcohol and 2) measure the alcohol levels in an individual to determine intoxication. Court and legal systems have a constant need and responsibility to test

individuals for alcohol use. Additionally, members of society have a responsibility to not drive while intoxicated. A patch or device that an individual could wear to determine if they are above or below the legal limit could be advantageous. Measurement and treatment of alcohol use has largely relied on breath, blood, and urine testing. However, the fluid just beneath an individual's skin (interstitial fluid (ISF)) could also be used instead of blood since it can be gathered more rapidly and with much less pain, using a patch with very tiny needles (microneedles) on its underside. Bloodless ISF testing through a patch that can be worn could provide valuable information on alcohol exposure and be more tamper proof. Employees undergoing drug tests and rural populations may be more willing to adopt the practice using this less invasive method. Ideally, the system which can rapidly collect ISF and produce a reliable reading would eliminate the need for expensive laboratory tests and any concerns related to possible contamination in its chain of custody. Previous studies at UNM utilizing these microneedles for other applications in humans, suggest subjects feel little to no pain. Furthermore, the UNM team has used these microneedles to extract large quantities of ISF from humans and rats. The Derma-Tec team has previously developed alcohol measurement methods. The UNM and Derma-Tec teams will work together to add the alcohol measurement and microneedle ISF collection together and produce a microneedle patch that can be worn and measure alcohol in ISF. The researchers will initially collect ISF from 16 rats, add alcohol to the collected ISF, and measure the alcohol content. The researchers will then design new patch designs that will have alcohol detection built in, and these devices will be tested on up to 28 additional rats to develop a successful patch device that can be worn to detect alcohol consumption.

Returned for modification on 9/4/2019.

Discussion during the meeting: This protocol had not yet been returned for modifications so it was sent immediately for DMR. Add the species to the title. The reviewers will remain the same per the Vice-Chair.

Decision: Approved: Yes=11 No=0 Abstained=0 Recused=0

Item # 5 Major Amendments:

200657 - "Role of non-coding RNAs in brain development and function and antipsychotic treatment in mice."

Reviewers: *12, 27, AV*

A motion for approval was made and carried.

Summary: We are removing prenatal poly I:C injections and i.p. CXCR2 inhibitor injections and instead adding ip injections of antipsychotics (olanzapine, haloperidol, risperidone, and vehicle) in adult male and female (not pregnant) mice. Following a few weeks after daily IP injections mice will be euthanized and brains will be removed for molecular measurements of non-coding RNAs and other mRNAs. Prenatal valproic acid exposure remains in the protocol as before as well as postnatal ip injections with an exosomes inhibitor. As far as numbers, we are expecting the total number of mice to remain the same.

Sent for Pre-Review 1 on 8/21/2019.

Discussion during the meeting: The primary reviewer gave a summary of the protocol. This is a pilot study. The PI better clarified the scientific rationale including the use of exosomes. The PI also better described the use of the Valproic acid and any associated toxicity. One typo in the project design was corrected. There was a discussion about the scientific merit of the study and who performed the peer review (RAC). The PI will be applying for an RO1. The PI should

repeat one portion of the alternative search as suggested by the Research Librarian. The results can be placed in the alternative search narrative. This can be accomplished by DMR. The motion for approval was withdrawn and a motion for approval for DMR was made and carried. The Research Librarian will be the sole DMR reviewer.
Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200714 - "Chemokine receptors in MRI contrast-induced organ fibrosis [a mouse model]".
Reviewers: *18, 23, AV*
A motion for approval was made and carried
Summary: Additional numbers of animals are requested, these animals will be randomized to a high fat or control chow diet. Preliminary data suggests that gadolinium exposure induces dyslipidemia while altering cardiac output. Obesity is a known risk factor for high cardiac output. Risk factors associated with gadolinium-induced disease (such as fibrosis) are entirely unexplored. We aim to examine the combinatorial impact of a high fat diet and gadolinium exposure in our rodent model. For that this experimental designed ask for160 mice. Our initial experimental does not include a high fat diet (HDF) on this proposal we add a group with HFD for total 24 week, and compare with control.
No extra distress or pain will be involve.
Recommended for approval on 9/3/19.
Discussion during the meeting: The secondary reviewer gave a summary of the protocol. This is a straightforward amendment to add a high fat diet and additional animals. The PI performed a new alternatives search to include the new diet during the pre-review but the search needs to be repeated with proper spelling and search terms. The motion for approval was withdrawn and a motion for approval for DMR was made and carried. The Research Librarian will be the sole DMR reviewer.
Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200717 DMR – "A mouse model of Mycobacterium abscessus lung infection that mimics human infection."
Reviewers: *22, 26, AV*
Summary: We desire to repeat our initial infection/immunology experiments with M. abscessus since we do not feel that the protocol is optimized to detect a difference between control and experimental mice in terms of M. abscessus lung infection based on our results. We are proposing three changes to our protocol in this amendment – 1) infect mice with M. abscessus 390R at 12 weeks post tamoxifen induction rather than at 6 weeks, 2) infect mice directly into the trachea using a microsprayer rather than via the intranasal route, 3) test three different infecting inocula to determine which is optimal for establishing productive lung infection, and 4) perform replicate immunology studies during this study. We are adding animals greater than 10%.
Approved as a DMR by Sub-Committee on 8/29/2019.

Item # 6 Minor Amendments:

200613 - "Mouse and Rat Models of Orofacial Nerve Injury, Back Pain and Visceral Pain for Preclinical Studies of Pain Mechanisms and Potential Therapeutics".
Reviewers: *Chair, AV*

Summary: We are requesting approval to add one additional experimental non-opioid therapeutic for testing in our previously approved mouse model of chronic orofacial pain: BPY-104. Testing this cellular stress inhibitor will provide better understanding of cellular stress and autophagy occurring during persisting pain potentially related to the neuronal circuitry alterations occurring in these limbic cortical regions during the chronification of pain.
We will not be requesting any additional animals; we will repurpose numbers from initially proposed experiments that were not performed due to changes in research objectives. We will not be requesting any changes to the previously approved models that would increase pain or distress to the animals. It is our hope that these drugs will prove to be therapeutic and relieve pain.
Approved by IACUC Chair and Attending Vet on 8/1/19.

200634 - "A breeding protocol to understand inflammatory diseases in a mouse model."
Reviewer: *AV*
Summary: Adding new strain, MSNASH, to breed a mouse model of metabolic syndrome for experimental procedures.
Approved by Attending Vet on 8/26/2019.

200641 - "A mouse model to study inflammatory diseases."
Reviewers: *Chair, AV*
Summary: Add/remove staff; this amendment intends to add the MS NASH mouse strain from Jackson laboratory. MS NASH strain is mouse model of metabolic syndrome. Metabolic syndrome (MetS) is characterized by the following risk factors: high blood sugar, high blood pressure, excess body fat around the waist and abnormal cholesterol levels. These risk factors can lead to an increase risk of heart disease, stroke, and type 2 diabetes. Recently, it has been shown MetS patient have an increase chance to be diagnosed with inflammatory bowel disease. Along with IBD, individuals who are obese or living with diabetes have been found to have a leaky gut (intestinal permeability). We believe intestinal macrophages and epithelial cells play a major role in regulating intestinal permeability. The increase in mice is to study the effects of metabolic syndrome on intestinal homeostasis, specifically intestinal macrophages and epithelial cells. I am planning to increase the number of mice to 107 animals and 96 of these mice will be progeny.
Approved by IACUC Chair and Attending Vet on 8/30/2019.

200728 - "Rodent models of pulmonary hypertension, intermittent hypoxia induced systemic hypertension and asthma."
Reviewer: *AV*
Summary: I'd like to add one more colony to this protocol the CB17SC, C.B-Igh1<b>/IcrTac-Prkdc<scid>. We will maintain up to 2 breeding pairs. We need these mice to perform the Tv-DTH test in our experimental protocol.
Approved by Attending Vet on 8/28/2019.

200789 - "Type 2 Immune Response, Thermogenesis and energy homeostasis - Mouse Model."
Reviewers: *Chair, AV*
Summary: To confirm the role of adiponectin in thermogenesis, we will compare the differences in response to cold stress between our adiponectin ko mouse line and another adiponectin mouse

line (*Adipoq*^{tm1Chan}). Thus, we will order 5 over 8-weeks male B6;129-*Adipoq*^{tm1Chan}/J (Stock No: 008195) mice and 5 male B6129SF2/J (Stock No: 101045) mice with same age from Jackson laboratory for metabolic phenotyping.
Approved by IACUC Chair and Attending Vet on 8/1/2019.

200790 - "Breeding Protocol for Autophagy Science Core (ASC) ".
Reviewer: *AV*
Summary: We are acquiring a new strain from another PI in the UK. We are receiving 2-3 breeding pairs of B6-Atg16 fl/fl mice. Adding this strain will increase our total number of animals by 8%. See attached animal numbers table.
Approved by Attending Vet on 8/22/19.

200822 - "Alcohol Research Center Scientific Core Breeding and Drug Exposure Protocol for Mice and Rats.
Reviewer: *Chair*
Summary: Add/Remove staff.
Approved administratively per IACUC Chair on 8/9/19.

200822 #2 - "Alcohol Research Center Scientific Core Breeding and Drug Exposure Protocol for Mice and Rats.
Reviewer: *Chair*
Summary: Add/Remove staff.
Approved administratively per IACUC Chair on 8/14/19.

200823 - "Murine Models to study the impact of the peritoneal immune environment on ovarian cancer progression and response to treatment - COMBINED PROTOCOL."
Reviewers: *Chair, AV*
Summary: Add/remove staff; add silica nanoparticles as a no antigen control for the cancer vaccine.
Approved by IACUC Chair and Attending Vet on 8/29/2019.

200831 - "Mouse Breeding protocol for Immunity and Inflammation Mechanisms."
Reviewer: *AV*
Summary: Add/remove staff; We request to add a stain B6,129,SJL-CisflxFoxp3CrexR26YFPs that contains a CD45.1 marker (+48), and reduce the number of B6-Igf1rflxCD4Cre (-48). Net change: 0. The number chart has been updated.
Approved by Attending Vet on 8/19/2019.

200833 - "Role of neuron-specific gene family in behavior."
Reviewers: *Chair, AV*
Summary: NSG1 and NSG2 KO animals will undergo a series of behavioral tests (see behavior section) once they have been genotyped and assigned to groups. Behavioral testing will occur during normal working hours (daytime). As mice are a nocturnal species they are most alert and active during the dark phase and previous studies have demonstrated improved behavioral performance on the tests proposed during this period. Thus, we propose that these animals be housed in rooms on reverse light-dark schedule.

Approved by IACUC Chair and Attending Vet on 8/30/2019.

200848 - "Mechanisms of hypoxic pulmonary hypertension in a mouse model."
Reviewers: *12 (VC), AV*
Summary: We would like to add Laser Speckle Contrast Imaging (LSCI) to complement the determination of inflammation in the TV-DTH assay in which we measure foot swelling using a caliper. LSCI is a method to instantly visualize microcirculatory tissue blood perfusion. It is a high speed and high resolution. It uses a laser light that does not cause
tissue damage. When laser light illuminates an object, the backscattered light will form an interference pattern consisting of dark and bright areas. This pattern is called a speckle pattern. If the illuminated object is static, the speckle pattern is stationary. When there is movement in the object, such as red blood cells in a tissue, the speckle pattern will change over time. Inflammation should cause increases in paw blood perfusion so, we hypothesize that LSCI would be able to measure increases in paw inflammation in the TV-DTH in a more reliable and sensitive way than the caliper. Another UNM PI owns a portable LSCI and he will lend it to us to use it in mice. Only associates listed in this protocol will handle the mice and perform the imaging.
Approved by Vice Chair and Attending Vet on 8/19/2019.

200883 - "Control of allergic airway inflammation - Mouse models."
Reviewers: *Chair, AV*
Summary: In responses to a paper reviewer, we need trace T cell fate in vivo and request to add a new strain B6,129,SJL-CisflxFoxp3CrexR26YFP (Cisfl/+) (+5, Cat# C) that will be paired with existing strain B6,129-CisflxFoxp3CrexR26YFP (Cisfl/fl) (+5, Cat# C) as donors and Rag1KO (+6, , Cat# D) as recipients for a transfer asthma experiment. Total increase, 16. The number chart has been updated.
Approved by IACUC Chair and Attending Vet on 8/19/2019.

200899 - "Role of Acid Sensing Ion Channel in the Vasculature."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 8/22/2019.

Item # 7 Annual Renewals:

200269 Closure - "Enhancement of Neurogenesis and Memory by a Neurotrophic Peptide in Traumatic Brain Injury."
Reviewer: *Chair*
Summary: This study and funding has ended. If we need another mouse TBI protocol, we will rewrite it.
Closed administratively per IACUC Chair on 8/1/2019.

200464 DMR - "Breeding and Holding Protocol for STEP KO mice and Fractalkine transgenic mice
Reviewer: *AV*
Approved as a DMR by Attending Vet on 8/29/2019.

200525 DMR by Chair – “Pulmonary immunization with BCG in mice."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 8/8/2019.

200604 Tissue Closure - "Rat Blood for Exosome Isolation " has been Submitted for Approval.
Reviewer: *Chair*
Summary: This protocol was to use excess rat blood from other approved protocols to optimize our exosome purification from blood. We were successful in this. We used a total of approximately 10-15 mL of rat blood and successfully isolated exosomes from the biofluid. We were also able to compare this to exosomes isolated from interstitial fluid (ISF) from other approved protocols. At this time, we do not wish to continue this protocol. Our other currently approved protocols include the collection and analysis of ISF and blood, making this protocol redundant.
Closed administratively per IACUC Chair on 8/26/2019.

200663 DMR by Chair - "Mouse models for studying the molecular mechanisms of gliogenesis and gliomagenesis".
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 8/13/19.

200720 DMR by Vet - "Breeding protocol for chemokine receptors in magnetic resonance imaging contrast-induced systemic fibrosis" has been Submitted for Approval.
Reviewer: *AV*
Approved as a DMR by Attending Vet on 8/13/19.

200722 20 DMR by Chair with Minor - "Targeting ErbB Receptors in Mouse Models of Cancer."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved as a DMR by IACUC Chair on 8/12/2019.

200724 Tissue DMR - "Blood- and tissue-related Discrimination of Infectious Disease Patterns."
Reviewers: *Chair, AV*
Approved by IACUC Chair and Attending Vet on 8/28/2019.

200733 Closure - "Pharmacokinetics of drugs encapsulated in dry powders when delivered by the pulmonary route in healthy rats."
Reviewers: *Chair*
Summary: We had used 12 Sprague Dawley rats to study the pharmacokinetics of an inhaled formulation (containing rifampicin, isoniazid, and verapamil encapsulated in hyaloronic acid polymer). The objective of this pilot study was to observe if hyaloronic acid polymer would allow the slow release of the drug(s) into the systemic compartment when delivered into the lung. Unfortunately, the analytical method used (HPLC) did not allow for the low detection of drug in the blood.

This study was part of an exchange student from the University of Parma, Italy. The student has left the laboratory since and we don't plan to continue studying this formulation in the future.
Closed administratively per IACUC Chair on 8/13/2019.

200757 DMR by Vet - "Breeding Protocol for Creation of CIRP transgenic mice".
Reviewer: *AV*
Approved as a DMR by Attending Vet on 8/14/19.

General Business:

1) IACUC Concerns – Semi-annual inspections are currently taking place (September 3-17, 2019).
2) HSC OLAW Assurance Renewal due by October 1, 2019
3) A focused, unannounced USDA Inspection took place on August 13 with no findings and USDA Registration Renewal due by October 18, 2019
4) CURES Act – the AV gave a summary of the recent proposed changes to the federal regulations to standardize requirements between federal regulators (USDA APHIS; PHS – OLAW; DoD; VA) with the goal to reduce administrative burden for compliance while sustaining animal welfare.

The meeting was adjourned at 1:32 PM.
Respectfully submitted by the Recording Secretary_____

HSC IACUC Meeting Minutes for Thursday, October 3, 2019
Meeting Place – [redacted]
Meeting time - 12:13 pm – 1:30 pm

Members Present
BHC Representative (NV)
Chair
Chemical Safety Rep (NV)
IACUC Administrator (NV)
Member #8
Member #17
Member #18
Member #20
Member #22
Member #25
Member #26
Member #27
Member #28 (Research Librarian)
OACC Operations Manager, Recording Secretary (NV)
Radiation Safety Representative (NV)

Members Absent
ARF Representative (NV)
Attending Veterinarian
EOHS Representative (NV)
Member #11
Member #12 (Vice-Chair)
Member #23
Member #24
SRS Rep (NV)

NV= non-voting members, consultant or staff

Per the request of the Vice-Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 9

Item # 1: Approval of Agenda:
A motion for approval of the October 3, 2019 agenda was made and carried. Protocol 200678 on page 11 was moved from the major to the minor amendments. The agenda was approved as amended.
Decision: Approved: Yes=9 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes:
A motion for approval of the September 5, 2019 meeting minutes was made and carried. The minutes were approved as presented.
Decision: Approved: Yes=9 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200605 3-yr RW DMR - "Time Course of Injury Mechanisms in a Rat Model of Acute Ischemic Stroke."
Reviewers: *12, 27, AV*
Summary: Presently, patients suffering stroke have only one treatment available, which is to open the clot in the blood vessel with the use of an enzyme tissue plasminogen activation (tPA) which has to be administered in less than 3 hrs after the stroke. Of the approximately 750,000 acute strokes per year in the US, about 30% of which are ischemic strokes, only 5% are treated with tPA for various reasons. An ischemic stroke develops when a blood vessel, supplying blood to an area of the brain, becomes blocked by a blood clot. The primary reason is that the time since the stroke started is unknown or the patients arrive beyond the 3 hr time window for the use of drugs to break up the blood clot (thrombolytic therapy). The fact that there is only one treatment for acute ischemic stroke despite the many drug and therapy trials conducted in patients and the hundreds of drugs shown effective in animals raises the question as to why this is the case. Where is the disconnect between the success of therapies in animals and the lack of translation to patients?
This problem is likely multifactorial. However, we identified two major reasons for this disconnect between animal and patient treatments for acute stroke. First, the animal models are by design, very reproducible whereas the strokes in patients are widely varying from very small strokes with little benefit from therapy and large devastating strokes that nothing would be able to improve outcome. Second, inherent in the concept of therapy for acute stroke is the notion that there is salvageable tissue that can be rescued by therapeutic intervention. The tissue that can be salvaged is known as the "Penumbra" which is generally thought of as the area surrounding the core or irreversibly damaged tissue as in an egg yolk surrounded by the white of the egg. However, the penumbra does not always occur this way. In 70% of the cases, the penumbra occurs as archipelagos within the core which complicates estimation of the volume of the penumbra or salvageable tissue. Differentiation of the penumbra volume from the core tissue volume cannot be done clinically due to the limitations of the clinical computer MRI or CT software. Thus, clinicians cannot determine the precise penumbra volume and this limitation in the clinical estimation of penumbra volume before therapeutic intervention in acute stroke in patients.
Returned for modifications on 8/5/2019.

200657 Major DMR - "Role of non-coding RNAs in brain development and function and antipsychotic treatment in mice."
Reviewers: *12, 27, AV*
Summary: We are removing prenatal poly I:C injections and i.p. CXCR2 inhibitor injections and instead adding ip injections of antipsychotics (olanzapine, haloperidol, risperidone, and vehicle) in adult male and female (not pregnant) mice. Following a few weeks after daily IP injections mice will be euthanized and brains will be removed for molecular measurements of non-coding RNAs and other mRNAs. Prenatal valproic acid exposure remains in the protocol as before as well as postnatal ip injections with an exosomes inhibitor. As far as numbers, we are expecting the total number of mice to remain the same.
Approved as a DMR by Sub-Committee on 9/6/2019.

200714 Major DMR - "Chemokine receptors in MRI contrast-induced organ fibrosis [a mouse model]".
Reviewers: *18, 23, AV*
Summary: Additional numbers of animals are requested, these animals will be randomized to a high fat or control chow diet. Preliminary data suggests that gadolinium exposure induces dyslipidemia while altering cardiac output. Obesity is a known risk factor for high cardiac output. Risk factors associated with gadolinium-induced disease (such as fibrosis) are entirely unexplored. We aim to examine the combinatorial impact of a high fat diet and gadolinium exposure in our rodent model. For that this experimental designed ask for160 mice. Our initial experimental does not include a high food diet (HDF) on this proposal we add a group with HFD for total 24 week, and compare with control.
No extra distress or pain will be involve.
Approved as a DMR by Sub-Committee on 9/26/2019.

200949 DMR - "Preserving the Ischemic Penumbra with a Drag Reducing Polymer."
Reviewers: *20, 24, AV*
Summary: In studies on anesthetized Sprague Dawley rats subjected to a stroke in the brain, we will determine whether a drug we have patented for the treatment of low blood flow in the brain will preserve and expand the ischemic penumbra which is tissue that is at risk because of low blood flow, but not yet dead, which would greatly increase the chances of effective therapeutic intervention and recovery. Studies testing neuroprotection in stroke have all failed in clinical trials because it was not until recently (2008) and later that it was realized that the patients suffering a stroke had to have a so-called ischemic penumbra (tissue under threat of dying but not yet dead) in order to show benefit with intra-arterial thrombectomy (IAT) where the clot is pulled out of the brain with a catheter. If the clot in the large vessel is retracted in time, the patient may suffer no brain damage. If successful in prolonging the duration of the ischemic penumbra or even increasing the size of the ischemic penumbra the patients are likely to benefit from either thrombolysis where an enzyme is injected to dissolve the clot or thrombectomy where the clot is pulled out.
Returned for modification on 7/31/2019.

200950 DMR - "Neurovascular Consequences of Inhaled Uranium Minesite-Derived Dusts in Mice."
Reviewers: *17, 26, AV*
Summary: Poor remediation of abandoned commercial uranium mines throughout the Southwestern United States has subjected Native tribal communities to metal-based (uranium, vanadium, arsenic) environmental exposures. There has also been an association between metal expsosure and autoimmune markers on these tribal lands. Recent data suggest that inhalation of fugitive mine-site derived dust may have neurovascular consequences in both healthy and autoimmune-prone individuals. People living within a few miles of such mine sites may be at risk of inhaling those dusts. To accomplish this, we will use a battery of exposure paradigms including a specially-designed mobile laboratory, contributed by colleagues at Michigan State University (AirCARE1), which houses rodents and permits exposure to dusts in the air around the lab. Mice will be exposed by inhalation to the dusts close to the mine site, and we will then explore the toxicity of these particles to the lungs, vasculature and brain in both wild type and

autoimmune-prone mice. These studies will provide important information about health risks of inhaled dusts for those living near these sites. These data will best serve policymakers in the National Institutes of Health and also the Environmental Protection Agency to make informed decisions relevant to public health. The proposed research intends explore this relationship and evaluate the mechanism underlying mine-site derived PM-induced endothelial dysfunction and long-term neurological consequences in both healthy and autoimmune-prone individuals.
Approved as a DMR by Sub-Committee on 9/13/2019.

200953 (change in PI) 3-yr RW DMR - "Training Protocol for Brain Recovery and Repair Preclinical Core."
Reviewers: *18, 23, AV*
Summary: It is critical that all personnel working with laboratory animals are trained in applicable methods associated with the species used and techniques required under their respective animal research programs. Assuring competence not only improves animal welfare and scientific integrity but also promotes research compliance. Procedures that will be trained under this protocol include: Basic handling, administration of anesthesia (injectable and inhalation), blood collection, agent dosing (oral, injectable via multiple routes – subcutaneous, intradermal, intraperitoneal, intravenous via tail vein or retro-orbitally, etc.), surgery to include sterile technique, euthanasia, necropsy for tissue collection,in-vivo electrophysiology (anesthetized and awake behaving animals), in-vivo imaging (anesthetized and awake behaving animals), and a variety of behavioral tasks (open-field, novel object recognition, cylinder task, Y-maze, Zero-maze, Morris water maze, touchscreen based learning and memory tasks, contextual fear conditioning, CatWalk gate analysis). To avoid pain or distress, anesthesia will be administered prior to conduct of potentially painful procedures and euthanasia will be administered after completion of invasive techniques such as surgery without them being allowed to recover from anesthesia, except when survival surgery is the primary training outcome. Laboratory mice are the primary models used in research at the Pre-Clinical Core and training is generally conducted using the target species, unless a viable non-animal model is available. Also, rather than purchasing or breeding animals solely for training, when possible, we will use rodents scheduled for euthanasia that were at end-points from survival research, retired breeders, or inappropriate genotype that are not useful for research.
Approved as a DMR by Sub-Committee on 9/18/2019.

200957 3-yr RW DMR - "Mechanisms of Neuronal Cell Death and Repair in Mouse Models of Stroke and Developmental Alcohol Exposure."
Reviewers: *20, 24, AV*
Summary: Project 1: Neural Stem Cells in Recovery and Repair Following Stroke. Stroke is a leading cause of long-term disability, with a high percentage of survivors requiring self-care assistance. This proposal is based on the scientific premise that adult neural stem cells (NSCs) contribute to plasticity and repair of the adult mammalian brain, and that enhancement of this regenerative response holds therapeutic promise in promoting long-term recovery of function following stroke. The focus of the current proposal is to elucidate the role of hypoxic signaling as a key regulatory mechanism in NSC function and the mechanisms by which endogenous NSCs promote revascularization and repair. These studies will utilize transgenic mice in which NSCs can be identified and genetically manipulated in a well-characterized model of ischemic stroke.

Project 2: Alcohol and Neurogenesis. Fetal alcohol spectrum disorder represents a significant health problem, with prevalence estimated to be as high as 4.5 per 1,000 live births. Despite this, few empirically supported interventions are available for mitigating the cognitive and behavioral disabilities associated with FASD. This work aims to identify novel therapeutic approaches to reverse learning deficits and hippocampal dysfunction. We are focused on hippocampal neurogenesis as a relevant target. These studies will utilize transgenic mice in which adult-generated neurons can be identified, quantified and electrophysiologically recorded from by fluorescent reporter expression in well-characterized models of prenatal alcohol exposure. In addition, we will determine how prenatal alcohol impacts oligodendrocyte function, including remyelination efficiency.
Project 3: SNAP 25 in network function: Adult neurogenesis is a form of brain plasticity that is important for certain forms of learning and memory. This research will investigate fundamental principles that are required for the proper integration and function of newborn neurons within an existing brain circuitry. It is hoped that this research will reveal fundamental knowledge important for enhancing cognition in aging and neurological disease, and in the context of brain repair. Here we will utilize a unique transgenic mouse in which SNAP-25, a protein required for synaptic transmission, is selectively knocked out of newborn dentate granule neurons in adult mice, thus genetically silencing these cells. This will allow us to figure out the role of these cells in hippocampal network activity under normal non-pathological conditions.
Approved as a DMR by Sub-Committee on 9/27/2019.

200959 DMR - "Rapid Alcohol Detection and Monitoring in Dermal Interstitial Fluid (ISF)."
Reviewers: *17, 8, AV*
Summary: Excessive alcohol consumption has numerous detrimental effects which can include heart, lung, reproductive, liver, and kidney problems. Alcohol consumption may also increase the likelihood of cancer. In addition to direct health concerns, excessive alcohol use may also develop into alcoholism and is also responsible for thousands of DWI fatalities each year in the United States alone. There is an urgent need for new testing devices that can 1) determine if an individual has consumed any alcohol and 2) measure the alcohol levels in an individual to determine intoxication. Court and legal systems have a constant need and responsibility to test individuals for alcohol use. Additionally, members of society have a responsibility to not drive while intoxicated. A patch or device that an individual could wear to determine if they are above or below the legal limit could be advantageous. Measurement and treatment of alcohol use has largely relied on breath, blood, and urine testing. However, the fluid just beneath an individual's skin (interstitial fluid (ISF)) could also be used instead of blood since it can be gathered more rapidly and with much less pain, using a patch with very tiny needles (microneedles) on its underside. Bloodless ISF testing through a patch that can be worn could provide valuable information on alcohol exposure and be more tamper proof. Employees undergoing drug tests and rural populations may be more willing to adopt the practice using this less invasive method. Ideally, the system which can rapidly collect ISF and produce a reliable reading would eliminate the need for expensive laboratory tests and any concerns related to possible contamination in its chain of custody. Previous studies at UNM utilizing these microneedles for other applications in humans, suggest subjects feel little to no pain. Furthermore, the UNM team has used these microneedles to extract large quantities of ISF from humans and rats. The Derma-Tec team has previously developed alcohol measurement methods. The UNM and Derma-Tec teams will work together to add the alcohol measurement and microneedle ISF collection together and produce a

microneedle patch that can be worn and measure alcohol in ISF. The researchers will initially collect ISF from 16 rats, add alcohol to the collected ISF, and measure the alcohol content. The researchers will then design new patch designs that will have alcohol detection built in, and these devices will be tested on up to 28 additional rats to develop a successful patch device that can be worn to detect alcohol consumption.
Approved as a DMR by Sub-Committee on 9/12/2019.

Item # 4 New Protocols:

200938 - "Preclinical development of subunit tularemia vaccines in F344 rat model."
Reviewers: *11, 25, AV*
A motion for approval was made and carried.
Summary: The goal of this project is to develop a new subunit vaccine against pneumonic tularemia. A subunit vaccine contains only pieces of the disease-causing bacteria or virus, and is generally considered safer than other vaccines. We recently showed that when 2 different parts of the bacteria that causes tularemia, namely *Francisella tularensis*, is combined with a derivative of high density lipoprotein (HDL, the good cholesterol) and a substance that promotes immune responses, the resulting subunit vaccine protected Fischer 344 rats (a model of human tularemia) against lethal disease. We want to generate additional data in the rat model to support further development of the vaccine. We will perform 2 types of studies to 1) demonstrate that the vaccine prevents or reduces disease severity by exposing vaccinated rats to the disease-causing bacteria and 2) characterize the protective host response and immune mechanism of protection by collecting and analyzing blood and tissue samples from vaccinated rats before and after exposure to the bacteria.
Sent for Pre-Review 2 on 9/25/2019.
Discussion during the meeting: The secondary reviewer gave a summary of the protocol. This is a straight forward proposal. The review comments were all addressed during the pre-review. There were no further issues and the protocol was recommended for approval.
Decision: Approve: Yes=9 No=0 Abstained=0 Recused=0

200960 - "Mouse Breeding Protocol - Cargo Of Exosomes and Microvesicles In Tuberous Sclerosis Complex."
Reviewer: *AV*
Summary: Tuberous sclerosis complex (TSC) is caused by mutations in either the TSC1 (Hamartin) or TSC2 (Tuberin) genes and affects over one million people world-wide. Over 80% of young patients and all postmortem samples were found to have renal disease, most commonly renal tumors (angiomyolipomas) and kidney cysts. The latter develops in nearly half of patients with TSC and is associated with a significant likelihood of early kidney function loss. We seek to address the mechanistic and molecular basis of kidney cyst formation and develop new therapies to reduce the severity of kidney disease in TSC. Our hypothesis is that in TSC kidney cysts grow aberrantly in genetically normal cells and this this growth is due to abnormal exosomes (small cell free particles) and their protein and nucleic acid cargo in the abnormal cell growth that causes kidney cysts to form in TSC.
Approved as a DMR by Attending Vet on 9/19/2019.

200962 3-yr RW - "GPER/GPR30 Estrogen Receptor in Mouse Models of Obesity and Metabolic Function."
Reviewers: *22, 26, AV*
A motion for approval was made and carried.
Summary: The course of Type 2 diabetes differs between the genders. Numerous studies have implicated estrogen as being protective in diabetes. Obesity is also a confounding factor in Type 2 diabetes. There are three receptors that can bind to estrogen, and our group is intensively studying the most recently described estrogen receptor called the G protein-coupled estrogen receptor, GPER, also known as GPR30. We are able to model diabetes associated with obesity in males and females (with and without ovariectomy to remove estrogen) using mice, a well-established diabetes model. Moreover we can take advantage of our mouse models lacking GPER through knockout technology to compare the effects in the absence of the GPER estrogen receptor. Finally, we can manipulate GPER activity in normal (wild type) mice using our GPER selective agonist (activator) G-1, and our GPER selective antagonist (inhibitor) G36. These approaches will leave other estrogen receptor pathways intact, so any results can be attributed to GPER.
For these studies, glucose tolerance tests (GTTs), insulin tolerance tests (ITTs), and pyruvate tolerance testst (PTT) will be performed. These tests measure the changes in blood glucose levels over a prescribed interval following the administration of a bolus of glucose (for the GTT), insulin (for the ITT). In addition, pyruvate tolerance tests (PTT), which indirectly measures gluconeogenesis in the liver (the generation of glucose from substrates such as lactate and glycerol), will be used. Mice exhibiting dysregulation in liver glucose metabolism (such as mice on a high fat diet) may exhibit higher glucose post pyruvate challenge. The test can be useful to determine if mice with altered expression of GPER exhibit differences in hepatic glucose regulation and also identify new therapeutic agents that can improve the hepatic glucose function. We will also investigate the ability of the GPER activator G-1 to dampen obesity due to the loss of another estrogen receptor called ERalpha, as well as in a mouse model of obesity, metabolic disease, and diabetes called MS-NASH that closely mimics the human syndromes. Finally, we will isolate hepatocytes from Wild type and GPER KO mice to study signaling pathways in culture.
Recommended for approval on 9/26/2019.
Discussion during the meeting: The primary reviewer gave a summary of the protocol. This is a well written renewal of a previous study. Several review comments were addressed during the pre-review. If the PI has not yet validated the conditional knock-out model, consider including the single Cre and the flox mice in the experimental design as controls. The PI should remove cardiovascular disease from their goals if they are not including it in this study. The lay abstract should be updated administratively via email after verification by the PI. The alternative search needs to be repeated with different search terms but this can be accomplished via email after approval per the Research Librarian. There were no further issues and the protocol was recommended for approval.
Decision: Approve: Yes=9 No=0 Abstained=0 Recused=0

200963 3-yr RW - "The role of the estrogen receptor GPER/GPR30 in carcinogenesis in mice."
Reviewers: *17, 8, AV*
A motion for approval was made and carried.

Summary: Estrogen is a critical hormone in the human body because it regulates the growth, development and homeostasis of numerous tissues. The best understood roles of estrogen are the regulation of mammalian reproduction and breast function. Estrogen plays a critical role in the development of normal breast and uterine tissue, and in addition stimulates proliferation in estrogen-responsive breast and uterine tumors. For this reason, compounds that interfere with estrogen function are an important treatment for estrogen-responsive cancers. We have recently characterized a novel estrogen receptor (GPER, for G Protein-coupled Estrogen Receptor, also called GPR30) that we hypothesize functions alongside the traditional estrogen receptors (ER alpha and ER beta) to regulate physiological responsiveness to estrogen. Our results also demonstrate that some compounds that interfere with classic estrogen receptors, and that are used to treat breast cancer (such as tamoxifen), can actually activate GPER. Characterizing GPER function will therefore contribute to our understanding of estrogen-induced growth and proliferation in normal physiology and cancer progression.
Our goals are to understand how GPER functions as an estrogen receptor – in other words, to what cellular functions does GPER contribute? Using our GPER-specific activators and inhibitors, we can now begin to dissect the function of GPER in normal physiology. Furthermore, we have mouse models that lack GPER, or that overexpress GPER in the breast, and these can also be used to understand the function of this receptor. Typically, estrogen is thought to influence female reproduction and breast development, but it also regulates a multitude of other functions, including male reproduction, cardiovascular development, immune function, bone density, brain function, etc. Furthermore, estrogen also promotes breast and endometrial cancer, and may be implicated in ovarian cancer. We do not propose to address all of the possible functions of GPER here, however our treatment protocols allow us to study multiple organ systems from one animal.
One of our goals is to characterize GPER function so we can understand if and how it might participate in both normal development and cancer. We hypothesize that GPER promotes estrogen-dependent tumorigenesis in cells and tissues that express GPER. It is known that interfering with estrogen binding to ERalpha and ERbeta can inhibit growth, and drugs that do this are often effective cancer therapies. One of our goals is to identify drugs that interfere with estrogen binding to GPER and then test these to see if they might be effective agents to detect GPER-rich tumors, and/or effective cancer therapies in tissues rich in GPER.
Sent for Pre-Review 1 on 9/17/2019.
Discussion during the meeting: The primary reviewer gave a summary of the protocol. This is a well written renewal of a previous study. There are multiple studies described in this protocol. A flow diagram (or a few diagrams) would be helpful in this case. The PI can provide via email. The review comments were all addressed during the pre-review. There were no further issues and the protocol was recommended for approval.
Decision: Approve: Yes=9 No=0 Abstained=0 Recused=0

200965 3-yr RW - "A rodent model of chronic hypoxic pulmonary hypertension."
Reviewers: *12, 27, AV*
A motion for approval was made and carried.
Summary: 1. What is the major problem being addressed by this study?
The job of your lungs is to transport oxygen from the air you breathe into your bloodstream while taking away carbon dioxide. When your lungs do not get enough oxygen, the blood vessels in the lung become narrowed, blocked or destroyed. This makes it harder for blood to flow

through your lungs and raises the pressure within the vessels of your lung. As the pressure builds, your heart works harder to pump blood through your lungs, which causes your heart muscle to weaken and fail. This serious condition becomes worse over time and sometimes results in death. The major problem that we will address in this study is that there are currently no cures for this disease.
2. What specific questions are we asking and how will we attempt to answer them?
Our goal is to find the events that lead to increased pressure within the vessels of the lung. To do this we need to understand how the blood vessels in the lung become narrowed, blocked or damaged. Once we discover what causes the blood vessels in the lung to narrow, we can give drugs to prevent that narrowing and see if that prevents the increased pressure in the lung and heart failure.
3. What is the potential overall impact of this work to the scientific community?
The increase in pressure within the blood vessels of the lung is called pulmonary hypertension. Treatments for pulmonary hypertension are limited, and at this time there is no cure. The planned studies will advance our knowledge of the mechanisms of pulmonary hypertension with the ultimate goal of allowing development of new treatments for this disease.
Sent for Pre-Review 2 on 9/30/2019.
Discussion during the meeting: The Chair gave a summary of the protocol. The lay summary was very clear and easy to understand. This is a well written renewal of a previous study. The AV suggested using a pre-emptive subcutaneous local anesthetic since systemic analgesic would affect study results. One term needs to be added to the alternative search. This can be accomplished administratively via email per the Research Librarian. The review comments were all addressed during the pre-review. There were no further issues and the protocol was recommended for approval.
Decision: Approve: Yes=9 No=0 Abstained=0 Recused=0

200968 Tissue - "PTSD mouse model animal behavior studies."
Reviewers: *Chair, AV*
Summary: Using the information gained from these mice we hope to be able to look at human PTSD in ways that are more biologically and clinically useful. We hope to better identify windows for therapy. We hope that these mice can tell us which of the human SERT gene variants are more protective against the clinical problems caused by PTSD. And which might make people more at risk to PTSD. All live experimentation has been concluded since January 2016 and this project is now in the analysis and microscopy stage.
Sent for IACUC Chair and Attending Vet Review #2 on 10/3/2019.

200969 3 yr RW - "Hypothermic Suppression Thresholds of Cortical Spreading Depression (CSD) in Rats ".
Reviewers: *20, 24, AV*
A motion for DMR was made and carried.
Summary: When the brain is injured it causes bursts of abnormal electrical activity in the brain that markedly increases the energy needs of the brain. When this occurs in the brain after injury, it creates a huge demand for oxygen and nutrients at a time when the brain and blood flow to it is compromised. Reducing brain temperature (hypothermia) is one way of reducing the needs of the brain for oxygen and nutrients. We plan to determine how much of a decrease in brain temperature is required to stop the abnormal brain electrical activity from occurring. We will be

performing surgical procedures on rats under surgical anesthesia and insert electrodes into their brains to measure the electrical activity that represents the abnormal activity and determine whether we can suppress this activity by decreasing brain temperature.
In addition to the acute studies described above we will allow the animals to recover from surgery with evaluation of the brain by MRI and behavioral recovery by various tests including rotarod, catwalk, Y-Maze, and shock avoidance. At the end of the studies the brains will be perfused fixed and stained with Fluoro-jade and H&E.
Returned for modification on 9/20/19.
Discussion during the meeting: The PI responses had not yet been received so this protocol was voted for DMR. The reviewers will remain the same per the Chair.
Decision: Approval for DMR: Yes=8 No=0 Abstained=0 Recused=1

200970 DMR - "Molecular Determinants of Brain Invasion and Metastasis in Mice Models."
Reviewers: *20, 24, AV*
Summary: Melanoma and breast cancer brain metastasis is an important cause of morbidity and mortality, and mechanisms responsible for their malignant progression to brain remain largely unknown. Circulating tumor cells (CTCs), "seeds" of fatal metastasis, are shed from primary/metastatic tumors, display great heterogeneity and plasticity, partially driven by the accumulation of genetic changes, but also by the recruitment and interactions with other cell types. During periods of metastatic latency, CTCs undergo spatial and temporal selection pressures which may lead to recurrent cancer death. Targeting CTCs by promoting their prolonged quiescent/growth-arrested state can be a promising strategy to overcome cancer metastasis, notably to brain. Therefore, it is fundamental to understand the molecular determinants of brain-metastatic disease and to use this knowledge for developing novel therapies to predict and/or prevent brain metastasis.
Sent for DMR by Sub-Committee on 9/30/2019.

Item # 5 Major Amendments:

200653 DMR - "A Mouse Model for Mechanisms of Immune Dysregulation Produced by Uranium, Arsenic, and Metal Mixtures (Biomedical Project (BP2), Superfund Center)."
Reviewers: *18, 23, AV*
Summary: Add/remove staff: Increase animals greater than 10% - we received a supplemental award to examine the microbiome and immune system in the GI tract of mice exposed to uranium and/or arsenic so we are adding an additional 120 mice to the protocol.
Approved as a DMR by Sub-Committee on 9/26/2019.

200744 DMR - "Rodent MRI Service for External Contracts."
Reviewers: *11, 25, AV*
Summary: Change in Principal Investigator.
Approved as a DMR by Sub-Committee on 9/26/2019.

Item # 6 Minor Amendments:

200600 - "Non-invasive Imaging and Irradiation Optimization by the Animal Models Shared Resource."

Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 9/25/19.

200613 - "Mouse and Rat Models of Orofacial Nerve Injury, Back Pain and Visceral Pain for Preclinical Studies of Pain Mechanisms and Potential Therapeutics."
Reviewers: *Chair, AV*
Summary: We are requesting approval for the addition of a non-surgical, commonly used protocol to stimulate immune responses. We would like to immunize 20 of our BALB/c mice with small peptides in order to provide tissue to a collaborator who will create single chain variable fragment (scFv) antibodies directed against proteins we are investigating. We will vaccinate with 4 different peptides: small proline rich protein 1a (SPRR1A), transcription factor SRY-Box 11 (SOX11), Listeria PrsA2, and S. pneumoniae PrsA . The Sprr1a and Sox11 peptides are small portions of endogenous human proteins. The listeria and pneumonia peptide fragments are <20 a.a. sequences of these large proteins. We will use 5 BALB/c mice for each peptide, male 6-8 weeks old. Ten ug of peptide will be mixed with 10 ug of Imject alum and injected i.p. on days 0, 21, and 42. On day 56, mice will be euthanized, terminal blood drawn via cardiac puncture, and spleens will be removed for RNA isolation. We anticipate no adverse effects other than the momentary discomfort caused by i.p. injection techniques. No additional mice are requested.
Approved by IACUC Chair and Attending Vet on 9/19/2019.

200786 - "Breeding and holding protocol for GluN2A KO mice".
Reviewer: *AV*
Summary: One new strain is being added: COX2 loxp mice (COX2 fl/fl mice).
Approved by Attending Vet on 8/30/2019.

200800 - "A Rodent Model of Sleep Apnea-Induced Pulmonary Hypertension."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 9/9/2019.

200802 - "Alcohol and developing neuronal circuits: characterization using mice".
Reviewers: *Chair, AV*
Summary: We request authorization to perform contextual fear conditioning experiments to assess function of the retrosplenial cortex. We found that vapor chamber exposure during postnatal day 7 causes apoptotic neurodegeneration in this brain region, which is required for the acquisition and retention of contextual fear memory. There will be no increase in the number of animal needed, as mice will be subsequently used for other approved electrophysiological, immunohistochemical or behavioral experiments.
Approved by IACUC Chair and Attending Vet on 9/13/19.

200822 - "Alcohol Research Center Scientific Core Breeding and Drug Exposure Protocol for Mice and Rats."
Reviewers: *Chair, AV*

Summary: Add/remove staff; Three lines of mice are being added. These animals will be used in studies conducted by another PI and are funded as a Pilot Project in the New Mexico Alcohol Center NIAAA P50 grant. The lines being added are: OPC specific Pdgfra-CreER line: B6N.Cg-Tg(Pdgfracre/ERT)467Dbe/J 018280, Astrocyte specific Aldh1l1-CreER line : B6N.FVB-Tg(Aldh1l1-cre/ERT2)1Khakh/J 029655, Ribo-TAG line B6N.129-Rpl22tm1.1Psam/J Jax stock 011029. The number of animals in Pain Category C has been increased by 80. The breeding plan is that the Ribo-TAG will be females (N=40), N=20 for each CreER line. Half the breeding females will be exposed to ethanol and the others will serve as saccharin controls.
Approved by IACUC Chair and Attending Vet Review on 9/26/2019.

200823 - "Murine Models to study the impact of the peritoneal immune environment on ovarian cancer progression and response to treatment - COMBINED PROTOCOL."
Reviewers: *Chair, AV*
Summary: Add/remove staff; To expand our silicified cell vaccine studies from prophylactic to therapeutic, we are adding alternative time points (in addition to the existing prophylactic time points); adding a definition of the source of the tumor cells used to create the silicified cancer vaccine to include “syngeneic and autologous" tumor cells; and adding ascites collection to the existing description of survival surgery in mice with ovarian cancer.
Approved by IACUC Chair and Attending Vet on 9/13/2019.

200830 - "Pharmacokinetics of clofazimine dry powders when delivered by the pulmonary route in healthy mice."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 9/4/2019.

200848 - "Mechanisms of hypoxic pulmonary hypertension in a mouse model."
Reviewers: *12 (VC), AV*
Summary: We would like to add a new strain of mice, G protein-coupled estrogen receptor (GPER) KO female mice, a total of 24 additional mice to this protocol in category D, and add a modification to the way right ventricular systolic pressure is recorded in the non-survival surgery. The rationale of the request is that previous studies have identified an inhibitory effect of estrogen on the development of CH-induced pulmonary hypertension in rats.
However, the estrogen receptor type mediating this response to estrogen has not been identified. In collaboration with two other PIs, we propose to test the hypothesis that estrogen mediates these protective effects via GPER. The proposed experiments will determine whether GPER deficient mice (covered under another PI’s current breeding protocol) are more susceptible to the development of CH-induced pulmonary hypertension compared to
wild-type female mice (WT). The purpose is to generate preliminary data for an NIH grant submission
Approved by Vice Chair and Attending Vet on 9/17/2019.

200884 - "Breeding protocol for ovarian cancer mouse models."
Reviewer: *Chair*
Summary: Add/remove staff.

Approved administratively per IACUC Chair on 9/16/2019.

Item # 7 Annual Renewals:

200369 DMR - "Repetitive Concussive Mild and Severe Traumatic Brain Injury Mechanisms and Treatment in Rats."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 9/17/2019.

200587 Closure - "Mechanisms and Application of Electrotherapy for Poststroke Depression."
Reviewer: *Chair*
Summary: We have kept this protocol active for the last two years, however, we are unsure if one of the staff members is coming back. When and if she gets back, we will resubmit the protocol.
Approved administratively per IACUC Chair on 9/20/2019.

200590 Closure - "Breeding Protocol in epithelial cancers."
Reviewer: *Chair*
Summary: PI has been unresponsive about this project. We notified him that this protocol would be closed if we did not hear from him.
Closed administratively per IACUC Chair on 9/12/2019.

200657 DMR – "Role of non-coding RNAs in brain development and function and antipsychotic treatment in mice."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 9/17/2019.

200678 - "Mouse Model for Glial and Glioma Development - Tamoxifen Administration & Electroporation."
Reviewer: *Chair, AV*
Summary: We are starting on a pilot project to study the effects of prenatal alcohol exposure (PAE) on glial development in the central nervous system. We want to transfer the animals for this pilot project to be exposed to alcohol administer under protocol # 16-200447-HSC for the New Mexico Alcohol Research Center. Breedings to generate these animals are covered under our protocol # 17-200663-B-HSC. Offspring that are generated following PAE will be transferred back to us to perform experiments, which will be covered under the current protocol. We anticipate transferring 40 breeding pairs (N=40 females and N=40 males) for PAE for the proposed pilot project, and a total of 240 offspring will be generated, 50% of which will be of the appropriate genotype to directly be used for experiments at various time points.
Returned for modification on 9/17/2019.

200734 DMR - "A Rat Model for Microsurgery Training."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 9/12/2019.

200744 - "Rodent MRI Service for External Contracts."

Reviewer: *Chair*
Summary: Add/remove staff.
Approved as a DMR by IACUC Chair on 9/17/2019.

200758 DMR by Chair "Characterization of the exosome and microRNA content of interstitial fluid in CD Hairless rats."
Reviewer: *Chair*
Species: Rat
Hazardous Agents: Isoflurane
Number of Authorized Animals:
Rat #1
USDA Category D - Alleviated Pain: 30
Approved as a DMR by IACUC Chair on 9/12/2019.

200769 DMR by Chair with Minor - "Study of T cell responses in a mouse model of influenza infection."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved as a DMR by IACUC Chair on 9/9/2019.

General Business:

1) IACUC Concerns –
    a. The committee reviewed and signed the semi-annual inspections and program review.
    b. Adverse Event – an adverse event occurred and was reported telephonically to OLAW. A written report will be submitted.
    c. IPRA request – UNM has received an IPRA request for list serve communications from TOPAZ.
2) HSC OLAW Assurance Renewal due by October 31, 2019.

The meeting was adjourned at 1:30 PM.
Respectfully submitted by the Recording Secretary_____

HSC IACUC Meeting Minutes for Thursday, November 7, 2019
Meeting Place – [redacted]
Meeting time - 12:21 pm – 1:11 pm

Members Present
Attending Veterinarian
BHC Representative (NV)
Chair
Chemical Safety Rep (NV)
IACUC Administrator (NV)
Member #8
Member #11
Member #12 (Vice-Chair)
Member #20
Member #22
Member #24
Member #25
Member #26
Member #28 (Research Librarian)
OACC Operations Manager, Recording Secretary (NV)

Members Absent
ARF Representative (NV)
EOHS Representative (NV)
Member #17
Member #18
Member #23
Member #27
SRS Rep (NV)
Radiation Safety Representative (NV)

NV= non-voting members, consultant or staff

Per the request of the Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 11

Item # 1: Approval of Agenda:
A motion for approval of the November 7, 2019 agenda was made and carried. The agenda was approved as presented.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes:
A motion for approval of the October 3, 2019 meeting minutes was made and carried. A name was removed from protocol 200587. The minutes were approved as amended.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200605 3-yr RW DMR - "Time Course of Injury Mechanisms in a Rat Model of Acute Ischemic Stroke."
Reviewers: *12, 27, AV*
Summary: Presently, patients suffering stroke have only one treatment available, which is to open the clot in the blood vessel with the use of an enzyme tissue plasminogen activation (tPA) which has to be administered in less than 3 hrs after the stroke. Of the approximately 750,000 acute strokes per year in the US, about 30% of which are ischemic strokes, only 5% are treated with tPA for various reasons. An ischemic stroke develops when a blood vessel, supplying blood to an area of the brain, becomes blocked by a blood clot. The primary reason is that the time since the stroke started is unknown or the patients arrive beyond the 3 hr time window for the use of drugs to break up the blood clot (thrombolytic therapy). The fact that there is only one treatment for acute ischemic stroke despite the many drug and therapy trials conducted in patients and the hundreds of drugs shown effective in animals raises the question as to why this is the case. Where is the disconnect between the success of therapies in animals and the lack of translation to patients?
This problem is likely multifactorial. However, we identified two major reasons for this disconnect between animal and patient treatments for acute stroke. First, the animal models are by design, very reproducible whereas the strokes in patients are widely varying from very small strokes with little benefit from therapy and large devastating strokes that nothing would be able to improve outcome. Second, inherent in the concept of therapy for acute stroke is the notion that there is salvageable tissue that can be rescued by therapeutic intervention. The tissue that can be salvaged is known as the "Penumbra" which is generally thought of as the area surrounding the core or irreversibly damaged tissue as in an egg yolk surrounded by the white of the egg. However, the penumbra does not always occur this way. In 70% of the cases, the penumbra occurs as archipelagos within the core which complicates estimation of the volume of the penumbra or salvageable tissue. Differentiation of the penumbra volume from the core tissue volume cannot be done clinically due to the limitations of the clinical computer MRI or CT software. Thus, clinicians cannot determine the precise penumbra volume and this limitation in the clinical estimation of penumbra volume before therapeutic intervention in acute stroke in patients.
Sent for DMR 1 on 11/4/2019.

200949 DMR - "Preserving the Ischemic Penumbra with a Drag Reducing Polymer."
Reviewers: *20, 24, AV*
Summary: In studies on anesthetized Sprague Dawley rats subjected to a stroke in the brain, we will determine whether a drug we have patented for the treatment of low blood flow in the brain will preserve and expand the ischemic penumbra which is tissue that is at risk because of low blood flow, but not yet dead, which would greatly increase the chances of effective therapeutic intervention and recovery. Studies testing neuroprotection in stroke have all failed in clinical trials because it was not until recently (2008) and later that it was realized that the patients suffering a stroke had to have a so-called ischemic penumbra (tissue under threat of dying but not yet dead) in order to show benefit with intra-arterial thrombectomy (IAT) where the clot is pulled out of the brain with a catheter. If the clot in the large vessel is retracted in time, the patient may suffer no brain damage. If successful in prolonging the duration of the ischemic

penumbra or even increasing the size of the ischemic penumbra the patients are likely to benefit from either thrombolysis where an enzyme is injected to dissolve the clot or thrombectomy where the clot is pulled out.
Sent for DMR 2 on 11/4/2019.

200968 Tissue - "PTSD mouse model animal behavior studies."
Reviewers: *Chair, AV*
Summary: Using the information gained from these mice we hope to be able to look at human PTSD in ways that are more biologically and clinically useful. We hope to better identify windows for therapy. We hope that these mice can tell us which of the human SERT gene variants are more protective against the clinical problems caused by PTSD. And which might make people more at risk to PTSD. All live experimentation has been concluded since January 2016 and this project is now in the analysis and microscopy stage.
Approved by IACUC Chair and Attending Vet on 10/8/2019.

200969 3 yr RW DMR - "Hypothermic Suppression Thresholds of Cortical Spreading Depression (CSD) in Rats ".
Reviewers: *20, 24, AV*
Summary: When the brain is injured it causes bursts of abnormal electrical activity in the brain that markedly increases the energy needs of the brain. When this occurs in the brain after injury, it creates a huge demand for oxygen and nutrients at a time when the brain and blood flow to it is compromised. Reducing brain temperature (hypothermia) is one way of reducing the needs of the brain for oxygen and nutrients. We plan to determine how much of a decrease in brain temperature is required to stop the abnormal brain electrical activity from occurring. We will be performing surgical procedures on rats under surgical anesthesia and insert electrodes into their brains to measure the electrical activity that represents the abnormal activity and determine whether we can suppress this activity by decreasing brain temperature.
In addition to the acute studies described above we will allow the animals to recover from surgery with evaluation of the brain by MRI and behavioral recovery by various tests including rotarod, catwalk, Y-Maze, and shock avoidance. At the end of the studies the brains will be perfused fixed and stained with Fluoro-jade and H&E.
Approved as a DMR by Sub-Committee on 10/17/2019.

200970 DMR - "Molecular Determinants of Brain Invasion and Metastasis in Mice Models."
Reviewers: *20, 24, AV*
Summary: Melanoma and breast cancer brain metastasis is an important cause of morbidity and mortality, and mechanisms responsible for their malignant progression to brain remain largely unknown. Circulating tumor cells (CTCs), "seeds" of fatal metastasis, are shed from primary/metastatic tumors, display great heterogeneity and plasticity, partially driven by the accumulation of genetic changes, but also by the recruitment and interactions with other cell types. During periods of metastatic latency, CTCs undergo spatial and temporal selection pressures which may lead to recurrent cancer death. Targeting CTCs by promoting their prolonged quiescent/growth-arrested state can be a promising strategy to overcome cancer metastasis, notably to brain. Therefore, it is fundamental to understand the molecular determinants of brain-metastatic disease and to use this knowledge for developing novel therapies to predict and/or prevent brain metastasis.

Approved as a DMR by Sub-Committee on 10/23/2019.

Item # 4 New Protocols:

200961 - "Understanding the Etiology of Head & Neck Cancer in Mice."
Reviewers: *12, 27, AV*
A motion for Approval for DMR was made and carried.
Summary: The purpose of this project is to understand head and neck cancer [Oral, Oropharyngeal and Laryngeal Squamous Cell Carcinoma (OPSCC)] at the molecular level using several animal models. With this information we can provide better diagnostics by finding markers that distinguish different types of OPSCC with different prognosis, and we can better understand the molecular pathways that drive this cancer, which could lead to new targets for therapy. By growing tumor cells and primary patient tumors in vivo, we will 1) provide an environment more relevant to that in which human tumors grow, allowing us to study molecular events that drive tumor growth, such as angiogenesis, or the growth of new blood vessels into solid tumors. Our second goal is to expand precious patient tumor tissue samples so they can be used in expanded experiments. To accomplish this we will use immunocompromised mice as incubators to amplify tumor material, then transplant the amplified tissue into new groups of mice for further expansion. We plan to conduct drug and radiation-based animal studies in order to identify new radiosensitizers which can hopefully be used to improve cancer control in humans. This will be done using patient-derived tumor xenografts (PDTX) as well as established OPSCC cell lines which will be used to conduct trials with investigational drugs. The expanded PDTX tissue can also be harvested for in vitro studies, increasing the number and relevance of in vitro tests.
Sent for Pre-Review 1 on 10/25/2019. Expires 11/28/2019.
Discussion during the meeting: The AV summarized the protocol. This is a well written 3-yr RW. There was one question about the pain categories that were selected but the AV agreed with the categories that were chosen by the PI. There were no PI responses yet but the protocol expires before the next convened meeting and the review comments so far were minimal so this was approved as a DMR by Sub-committee. Per the IACUC Chair, the reviewers will remain the same.
Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200973 3-yr RW DMR – "Spreading Depolarizations and Post-Ischemic Injury."
Reviewers: *18, 23, AV*
Summary: When a patient suffers a stroke, symptoms often get progressively worse over the first few days or week after the stroke starts. There are currently no treatments that can be given after the first few hours, to slow this progression that keeps going over the next few days. It was recently discovered that large waves of brain activation sweep through the brain, and cause the progressive injury. However, there are not yet treatments targeting these waves, and we don't know enough about them to suggest the most effective approaches. We are studying how to block those waves, or how to prevent the damaging consequences of these waves. We do this with two general approaches. The first is to study basic mechanisms of these waves in a simple preparation. After deeply anesthetizing mice, we remove the brain and then study these waves in thin slices of brain tissue. After brain slice preparation, these studies involve extensive analysis of excited tissues, recording neuronal activity and recovery after waves. The second general

approach is to study the waves in the brains of living, anesthetized mice, so that we can see them after being triggered by a stroke. While maintaining deep anesthesia, mice are prepared for imaging of waves through the intact skull, or by placement of electrodes into the surface of the brain. In all cases, animals are not allowed to recover from anesthesia, so there is no chance of pain or suffering arising from recovery of any surgeries. The benefits of the study include discovery of ways to prevent waves being initiated in stroke brain, and also ways to fortify brain so that the brain can recover from any waves that are not blocked. We are working closely with colleagues in the department of Neurosurgery, to ensure that approaches we develop are meaningful and can be moved into clinical use as quickly as possible.
Approved as a DMR by Sub-Committee on 10/24/2019.

200975 DMR – "Repeated Binge Alcohol Drinking and the Genetic Regulation of Neural Synchrony in Mice."
Reviewers: *20, 25, AV*
Summary: The proposed project will help researchers and clinicians better understand how genes regulate the behavioral and neural consequences of repeated binge alcohol consumption. The information gained from this research can be used to identify potential avenues for treating individuals with alcohol problems or those vulnerable to developing alcoholism; particularly those with increased risk due to genetic factors. Specifically, the proposed studies will reveal how the coordinated activity of networks of genes mediates the physiological functioning of a key brain reward circuit to facilitate repeated excessive alcohol consumption. This will result in a better understanding of why and how alcohol use leads to addiction and will help us develop strategies to prevent and treat excessive drinking.
Sent for DMR review on 10/30/2019.

200976 DMR - "Sin Nombre virus infection in deer mice."
Reviewers: *11, 24, AV*
Summary: Sin Nombre virus is a hantavirus that causes disease in humans. Sin Nombre virus is carried by deer mice. The virus replicates in these mice but does not make the mice sick. Humans can get infected when they breathe in aerosolized virus in the droppings of the mice. There are no drugs available for treating Sin Nombre virus infection. Some new research has found that certain proteins called antibodies can protect against infection from different hantaviruses, but this has not been tested for Sin Nombre virus. In this protocol we will test new antibodies against Sin Nombre virus by infecting deer mice and seeing if the antibodies block infection in the mice. To do this, we will construct an outdoor testing site at the Sevilleta National Wildlife Refuge where deer mice will be safely housed and infected with Sin Nombre virus. Antibodies will be tested to see if they can block infection in the deer mice. Also, different strains of Sin Nombre virus will be used to infect the deer mice in order to make virus stocks and to see if they replicate differently in the mice.
Returned for modification on 11/4/2019. Withdrawn by PI for now.

200979 DMR - "Mouse Breeding protocol for Imaging Mitochondrial Function in Excitotoxicity."
Reviewer: *AV*
Summary: This protocol will support breeding of the mouse genetic models defined herein and offspring will be transferred to applicable research protocols for the conduct of the research at 4-

8 weeks of age, or euthanized. Stroke is one of the leading causes of death and long-term disability in the United States. Unfortunately there are currently very few treatments to limit stroke damage, and are limited to a small sub-set of stroke sufferers. We are working to understand the mechanisms underlying the initiation and progression of stroke injury, in an attempt to suggest treatments that could be applied to many patients in the hours and days following a stroke, to prevent the spread of injury. One important contributor to injury is the waves of intense brain activation, which spread out from the initial site of the stroke injury. If these repetitive waves can be blocked, the final size of the injury is reduced, and the quality of life of stroke survivors is likely to be substantially increased. Unfortunately, there is a lack of interventions to target these spreading depolarization (SD) events.
In the course of our work, we have discovered that accumulation of zinc ions (Zn2+) can be a critical contributor to these events. Our ongoing work is centered on discovering the sources of Zn2+ that trigger brain injury, and how to prevent pathologic Zn2+ release. It is likely that the normal function of Zn2+ (released from nerve terminals) becomes over-activated during SD events, and contributes to injury. This protocol will enable breeding of mice that lack a specific Zn2+ transporter protein (ZnT3), which leads to selective elimination of Zn2+ from neurons, without affecting any of the other normal functions of Zn2+ functions in Zn2+. Tissues from these animals will be used to determine the source of Zn2+ that triggers brain injury. ZnT3 knockout does not lead to any observable behavioral phenotype, and colonies of animals homozygous for the deletion breed well and care for their offspring.
In addition to the examination of Zn2+, this protocol will support breeding of mice expressing the genetically encoded indicator GCaMP5g to enable studies that examine calcium dynamics during SD. Genetically encoded calcium indicators allow for chronic, non-invasive imaging of animals in vivo, as well as the imaging of neural populations rather than single cells at a high yield. We will be maintaining strains of mice that express either GCaMP5g or CaMKII-Cre. After breeding these two strains (GCaMP5g x CaMKII-Cre), the GCaMP indicator becomes activated (in a CaMKII-Cre dependent manner), and the offspring will then be utilized in experiments to enable the examinations of calcium-dependent injury following an SD event. These studies should identify new targets for stroke interventions, namely those that prevent excessive accumulation of calcium (and Zn2+) after passage of SD. The new work will also address mechanisms contributing to metabolic depletion after SD, and these studies are aimed at providing new strategies for increasing survival of neurons after multiple SDs in vulnerable brain tissue. Overall significance of this work is that it could provide a basis for new treatments for the progression of stroke injury, for which there is no current therapy and a great need.
Approved as a DMR by Attending Vet on 10/10/2019.

Item # 5 Major Amendments:

200678 - "Research Protocol: Mouse Model for Glial and Glioma Development - Tamoxifen Administration, Electroporation, Tumor Transplantation & Prenatal Alcohol Exposure."
Reviewers: *22, 26, AV*
A motion for approval was made and carried.
Summary: We plan to do tumor xenograft transplantation of mouse brain tumors to analyze rate of secondary tumor development. We have four different tumor types (1 control + 3 experimental conditions) which will be stereotactically injected into brains of NOD-SCID/NSG mice. We would like to request 40 additional NSG mice for this experiment. We are also starting

on a pilot project to study the effects of prenatal alcohol exposure (PAE) on glial development in the central nervous system. We want to transfer the animals for this pilot project to be exposed to alcohol administer under the New Mexico Alcohol Research Center protocol. Breedings to generate these animals are covered under our breeding protocol. Offspring that are generated following PAE will be transferred back to us to perform experiments on, which will be covered under the current protocol. We anticipate transferring 40 breeding pairs (N=40 females and N=40 males) for PAE for the proposed pilot project, and approximately a total of 240 offspring will be generated, 50% of which will be of the appropriate genotype to directly be used for experiments at various time points.

Recommended for approval on 10/23/2019.

Discussion during the meeting: The primary reviewer gave a summary of the protocol. This is an amendment to add two new aims. There were some questions about how the animals will be transferred back and forth between the experimental protocol and the breeding protocol. The PI should clarify the age at which pups will receive experimental treatments (before or after weaning) because that will in part, determine whether or not dams will need to be listed on the experimental protocol. The PI should also clarify the attached experimental design for these new aims. It would be helpful to have a flowchart of the time points for each project. There was a question about the use of plasmids and recombinant materials in this protocol. An IBC protocol will be required. The motion for approval was withdrawn and a motion for approval for DMR was made and carried. Per the IACUC Chair, the reviewers will remain the same with the addition of the Biosafety Rep.

Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200822 DMR - "Alcohol Research Center Scientific Core Breeding and Drug Exposure Protocol for Mice and Rats."
Reviewers: *12, 27, AV*
Summary: Change in PI.
Approved as a DMR by Sub-Committee on 10/8/2019.

200823 - "Murine Models to study the impact of the peritoneal immune environment on ovarian cancer progression and response to treatment - COMBINED PROTOCOL."
Reviewers: *17, 8, AV*
A motion for approval was made and carried.
Summary: In this amendment, we add a new aim to determine the estrogen effect on the tumor immune microenvironment and response to immune therapies. We plan to accomplish this by comparing outcomes in mice with intact ovaries with those of ovariectomized mice. Before the inoculation of ovarian cancer cells into the peritoneal cavity, mice will be ovariectomized. Anti-tumor immune responses during immunomodulatory treatment will be evaluated weekly by monitoring the tumor burden using IVIS imaging system.
We request to add a new procedure (ovariectomy) to our original animal protocol approved for ovarian cancer mouse models and survival surgery (to examine the impact of mock surgery onto peritoneal immune system). We will learn ovariectomy from a doctor who has been doing these under the protocol (19-200962-HSC). Although ovariectomy surgery will add pain/distress to mice, we will monitor mice to reduce postoperative pain and distress by the administration of buprenorphine.

The brief experimental plan is to perform ovariectomy to 6-8 wks age of females and after 2 weeks of post-operation recovery, mouse ovarian cancer cell line will be inoculated into the peritoneal cavity. As a pilot experiment, we will examine lymphocytes composition and their functional activity after ovariectomy. Next, we will set experiments to examine the difference in the responses to immune-modulatory treatment by flow analysis and survival study of tumor inoculated mice with/without ovariectomy. Our original protocol is included pain/distress category D for tumor-bearing mice survival study with the endpoint where mice show irreversible moribund state or accumulation of ascites with >30g bodyweight. Through the whole experiment, mice will be under the pain/distress category D.

Recommended for approval on 10/28/2019.

Discussion during the meeting: The AV and the Chair gave a summary of the protocol. This is a very well written and straightforward amendment. All of the review comments had been addressed during the pre-review and there were no additional concerns so the protocol was recommended for approval.

Decision: Approve: Yes=11 No=0 Abstained=0 Recused=0

Item # 6 Minor Amendments:

200594 - "Understanding the Etiology of Head & Neck Cancer." \
Reviewers: *Chair, AV*
Summary: We will be using 2 drugs (cobimetinib and trametinib) that we have not previously used in our lab. These drugs are FDA-approved and have been used in multiple studies of various tumor types in mice. In humans these drugs are generally delivered via the oral route which is why we wish to add oral gavage to our drug delivery methods.
Approved by IACUC Chair and Attending Vet on 10/14/2019.

200613 - "Mouse and Rat Models of Orofacial Nerve Injury, Back Pain and Visceral Pain for Preclinical Studies of Pain Mechanisms and Potential Therapeutics."
Reviewer: *Chair, AV*
Summary: We are requesting approval for the addition of a sciatic nerve survival-surgery that will induce a long-lasting model of chronic pain in mice. The surgery involves a ligation and cutting of the common peroneal and tibial nerves in the mouse's left hindlimb, while sparing the sural nerve. The model persists for many weeks after its induction. This model will be used in conjunction with our other pain models as a comparative to help understand the mechanisms underlying chronic pain.
We will be comparing the effects of the ketogenic high-fat diet versus normal chow in this spared nerve injury model. This diet is a modified version of our already approved Lieber-DiCarli diet, without the addition of the alcohol from the formula. This diet has been theorized to reduce allodynia and promote peripheral nerve growth. The pain-related behaviors of animal on the ketogenic diet will be compared to animals on normal mouse chow.
We will not be requesting any additional animals; we will repurpose numbers from initially proposed experiments that were not performed due to changes in research objectives. We will not be requesting any changes to the previously approved models that would increase pain or distress to the animals.
Approved by IACUC Chair and Attending Vet on 10/23/2019.

200795 - "Targeting aberrant signaling pathways in mouse xenografts of human acute lymphoblastic leukemia."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 10/15/2019.

200800 - "A Rodent Model of Sleep Apnea-Induced Pulmonary Hypertension."
Reviewer: *12 (VC)*
Summary: Add/remove staff.
Approved administratively per Vice-Chair on 10/14/2019.

200822 - "Alcohol Research Center Scientific Core Breeding and Drug Exposure Protocol for Mice and Rats."
Reviewers: *Chair, AV*
Summary: We request authorization to collect blood from the retro-orbital sinus for blood alcohol level determination. Retro-orbital blood collection was chosen over other collection methods because it has been shown to be the least stressful method compared to other methods in mice (Tsai et al., Lab Anim (NY). **2015** Aug;44(8):301-10), and because ethanol concentration collected using this method more accurately reflects brain concentrations (Gentry Physiol Behav. 1983 Oct;31(4):529-32).
Approved by IACUC Chair and Attending Vet on 10/31/2019.

200872 - "Molecular Regulation of T cell migration."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 10/31/2019.

200886 - "Mouse Breeding Protocol for Studies on the Effect of Alcohol Exposure on Brain Development."
Reviewer: *AV*
Summary: We request authorization to breed B6.129P2-Hrh3tm1TWl/J mice (histamine receptor type-3 knockout mice) to be used to validate antibodies against this receptor.
Approved by Attending Vet on 10/8/2019.

200956 - "Evaluate the Effect of Microenvironment on Tungsten-enhanced Breast Cancer Metastasis to the Lung using Orthotopic Mammary Cancer Mouse Models."
Reviewers: *Chair, AV*
Summary: Add/remove staff; Add animals (10%) and due to an error calculation on animal numbers sheet, move 12 mice from pain category C to pain category D.
Approved by IACUC Chair and Attending Vet on 10/18/2019.

200965 - "A rodent model of chronic hypoxic pulmonary hypertension."
Reviewers: *12 (VC), AV*
Summary: Add/Remove staff. This is a request related to Project 2 (Role of G protein-coupled estrogen receptor (GPER) in chronic hypoxia (CH)-induced pulmonary hypertension) to include a vaginal lavage protocol in female mice and rats to determine their stage in the estrous cycle.

Knowing their stage in the estrous cycle is important because some of the hemodynamic variables to be measured may be influenced by the changes in circulating ovarian hormones that occur during this cycle.
Approved by Vice-Chair and Attending Vet on 10/8/2019.

Item # 7 Annual Renewals:

200606 Closure - "Tissue Protocol for Spreading Depolarization in Peripheral Tissues."
Reviewer: *Chair*
Summary: The plan for this study was to use the extra gastrointestinal tissue from the animals that were assigned to the depolarization protocol. It was thought that perhaps there were waves of neuronal activation that occur in the nervous system of the intestine. We never did any of the experiments to prove this hypothesis.
Closed administratively per IACUC Chair on 10/31/2019.

200669 DMR - "Murine model for autophagy as a barrier against inflammation and microbes."
Reviewers: *Chair*
Approved as a DMR by IACUC Chair on 10/3/2019.

200708 Closure - "IL-6 Trans-signaling a Novel Therapeutic Target for Proliferative Vitreoretinopathy."
Reviewer: *12 (VC)*
Summary: Lack of funding.
Closed administratively per IACUC Chair on 10//2019.

200745 DMR - Spinal neuroimmune mechanisms underlying pain control: the role of prenatal alcohol exposure and identification novel or repurposed therapeutic targets to minimize peripheral neuropathy in rats and mice."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 10/7/2019.

General Business:

1) USDA Annual Reports due by December 1, 2019.
2) USDA Registration Renewal due by December 18, 2019
3) IPRA – we have received a second request from NEAVS.
4) Cisco VPN for TOPAZ login authentication is expiring by November 30, 2019. A new system for VPN will be implemented.
5) 21st Century CURES Act – this act hopes to reduce regulatory burden on institutions. The public comment period is over so we are just waiting to hear when this act will be finalized.
6) HSC OLAW Assurance Renewal was submitted.

The meeting was adjourned at 1:11 PM.
Respectfully submitted by the Recording Secretary_____

HSC IACUC Meeting Minutes for Thursday, December 5, 2019
Meeting Place – [redacted]
Meeting time - 12:15 pm – 1:08 pm

Members Present
Attending Veterinarian
BHC Representative (NV)
Chair
Chemical Safety Rep (NV)
EOHS Representative (NV)
IACUC Administrator (NV)
Member #8
Member #11
Member #12 (Vice-Chair)
Member #18
Member #20
Member #22
Member #24
Member #25
Member #27
Member #28 (Research Librarian)
OACC Operations Manager, Recording Secretary (NV)

Members Absent
ARF Representative (NV)
Member #17
Member #23
Member #26
Radiation Safety Representative (NV)
SRS Rep (NV)

NV= non-voting members, consultant or staff

Per the request of the Chair, the Recording Secretary noted a quorum was present.
Voting members at meeting start time = 11

Item # 1: Approval of Agenda:
A motion for approval of the December 5, 2019 agenda was made and carried. Item #3 "Discussion of consolidation of protocols for one PI", Item #4 "Pulse VPN Discussion", and Item #5 "IPRA Update" were added to the general business. The agenda was approved as amended.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 2: Approval of Minutes:

A motion for approval of the Thursday, November 7, 2019 meeting minutes was made and carried. The wording for protocol 200678 was changed from "An IBC protocol may be required" to "An IBC protocol will be required". The minutes were approved as amended.
Decision: Approved: Yes=11 No=0 Abstained=0 No=0 Recused=0

Item # 3: Old Business:

200605 3-yr RW DMR - "Time Course of Injury Mechanisms in a Rat Model of Acute Ischemic Stroke."
Reviewers: *12, 27, AV*
Summary: Presently, patients suffering stroke have only one treatment available, which is to open the clot in the blood vessel with the use of an enzyme tissue plasminogen activation (tPA) which has to be administered in less than 3 hrs after the stroke. Of the approximately 750,000 acute strokes per year in the US, about 30% of which are ischemic strokes, only 5% are treated with tPA for various reasons. An ischemic stroke develops when a blood vessel, supplying blood to an area of the brain, becomes blocked by a blood clot. The primary reason is that the time since the stroke started is unknown or the patients arrive beyond the 3 hr time window for the use of drugs to break up the blood clot (thrombolytic therapy). The fact that there is only one treatment for acute ischemic stroke despite the many drug and therapy trials conducted in patients and the hundreds of drugs shown effective in animals raises the question as to why this is the case. Where is the disconnect between the success of therapies in animals and the lack of translation to patients?
This problem is likely multifactorial. However, we identified two major reasons for this disconnect between animal and patient treatments for acute stroke. First, the animal models are by design, very reproducible whereas the strokes in patients are widely varying from very small strokes with little benefit from therapy and large devastating strokes that nothing would be able to improve outcome. Second, inherent in the concept of therapy for acute stroke is the notion that there is salvageable tissue that can be rescued by therapeutic intervention. The tissue that can be salvaged is known as the "Penumbra" which is generally thought of as the area surrounding the core or irreversibly damaged tissue as in an egg yolk surrounded by the white of the egg. However, the penumbra does not always occur this way. In 70% of the cases, the penumbra occurs as archipelagos within the core which complicates estimation of the volume of the penumbra or salvageable tissue. Differentiation of the penumbra volume from the core tissue volume cannot be done clinically due to the limitations of the clinical computer MRI or CT software. Thus, clinicians cannot determine the precise penumbra volume and this limitation in the clinical estimation of penumbra volume before therapeutic intervention in acute stroke in patients.
Approved as a DMR by Sub-Committee on 11/11/2019.

200678 DMR- "Research Protocol: Mouse Model for Glial and Glioma Development - Tamoxifen Administration, Electroporation, Tumor Transplantation & Prenatal Alcohol Exposure."
Reviewers: *22, 26, AV*
Summary: We plan to do tumor xenograft transplantation of mouse brain tumors to analyze rate of secondary tumor development. We have four different tumor types (1 control + 3 experimental conditions) which will be stereotactically injected into brains of NOD-SCID/NSG

mice. We would like to request 40 additional NSG mice for this experiment. We are also starting on a pilot project to study the effects of prenatal alcohol exposure (PAE) on glial development in the central nervous system. We want to transfer the animals for this pilot project to be exposed to alcohol administer under the New Mexico Alcohol Research Center protocol. Breedings to generate these animals are covered under our breeding protocol. Offspring that are generated following PAE will be transferred back to us to perform experiments on, which will be covered under the current protocol. We anticipate transferring 40 breeding pairs (N=40 females and N=40 males) for PAE for the proposed pilot project, and approximately a total of 240 offspring will be generated, 50% of which will be of the appropriate genotype to directly be used for experiments at various time points.
Approved as a DMR by Sub-Committee on 12/2/2019.

200949 DMR - "Preserving the Ischemic Penumbra with a Drag Reducing Polymer."
Reviewers: *20, 24, AV*
Summary: In studies on anesthetized Sprague Dawley rats subjected to a stroke in the brain, we will determine whether a drug we have patented for the treatment of low blood flow in the brain will preserve and expand the ischemic penumbra which is tissue that is at risk because of low blood flow, but not yet dead, which would greatly increase the chances of effective therapeutic intervention and recovery. Studies testing neuroprotection in stroke have all failed in clinical trials because it was not until recently (2008) and later that it was realized that the patients suffering a stroke had to have a so-called ischemic penumbra (tissue under threat of dying but not yet dead) in order to show benefit with intra-arterial thrombectomy (IAT) where the clot is pulled out of the brain with a catheter. If the clot in the large vessel is retracted in time, the patient may suffer no brain damage. If successful in prolonging the duration of the ischemic penumbra or even increasing the size of the ischemic penumbra the patients are likely to benefit from either thrombolysis where an enzyme is injected to dissolve the clot or thrombectomy where the clot is pulled out.
Approved as a DMR by Sub-Committee on 11/12/2019.

200961 DMR - "Understanding the Etiology of Head & Neck Cancer in Mice."
Reviewers: *12, 27, AV*
Summary: The purpose of this project is to understand head and neck cancer [Oral, Oropharyngeal and Laryngeal Squamous Cell Carcinoma (OPSCC)] at the molecular level using several animal models. With this information, we can provide better diagnostics by finding markers that distinguish different types of OPSCC with different prognosis, and we can better understand the molecular pathways that drive this cancer, which could lead to new targets for therapy. By growing tumor cells and primary patient tumors in vivo, we will 1) provide an environment more relevant to that in which human tumors grow, allowing us to study molecular events that drive tumor growth, such as angiogenesis, or the growth of new blood vessels into solid tumors. Our second goal is to expand precious patient tumor tissue samples so they can be used in expanded experiments. To accomplish this we will use immunocompromised mice as incubators to amplify tumor material, then transplant the amplified tissue into new groups of mice for further expansion. We plan to conduct drug and radiation-based animal studies in order to identify new radiosensitizers which can hopefully be used to improve cancer control in humans. This will be done using patient-derived tumor xenografts (PDTX) as well as established OPSCC cell lines which will be used to conduct trials with investigational drugs. The expanded

PDTX tissue can also be harvested for in vitro studies, increasing the number and relevance of in vitro tests.
Approved as a DMR by Sub-Committee on 11/12/2019.

200975 DMR – "Repeated Binge Alcohol Drinking and the Genetic Regulation of Neural Synchrony in Mice."
Reviewers: *20, 25, AV*
Summary: The proposed project will help researchers and clinicians better understand how genes regulate the behavioral and neural consequences of repeated binge alcohol consumption. The information gained from this research can be used to identify potential avenues for treating individuals with alcohol problems or those vulnerable to developing alcoholism; particularly those with increased risk due to genetic factors. Specifically, the proposed studies will reveal how the coordinated activity of networks of genes mediates the physiological functioning of a key brain reward circuit to facilitate repeated excessive alcohol consumption. This will result in a better understanding of why and how alcohol use leads to addiction and will help us develop strategies to prevent and treat excessive drinking.
Approved as a DMR by Sub-Committee on 12/3/2019.

200976 DMR - "Sin Nombre virus infection in deer mice."
Reviewers: *11, 24, AV*
Summary: Sin Nombre virus is a hantavirus that causes disease in humans. Sin Nombre virus is carried by deer mice. The virus replicates in these mice but does not make the mice sick. Humans can get infected when they breathe in aerosolized virus in the droppings of the mice. There are no drugs available for treating Sin Nombre virus infection. Some new research has found that certain proteins called antibodies can protect against infection from different hantaviruses, but this has not been tested for Sin Nombre virus. In this protocol, we will test new antibodies against Sin Nombre virus by infecting deer mice and seeing if the antibodies block infection in the mice. To do this, we will construct an outdoor testing site at the Sevilleta National Wildlife Refuge where deer mice will be safely housed and infected with Sin Nombre virus. Antibodies will be tested to see if they can block infection in the deer mice. Also, different strains of Sin Nombre virus will be used to infect the deer mice in order to make virus stocks and to see if they replicate differently in the mice.
Returned for modification on 11/4/2019.

Item # 4 New Protocols:

200986 - "Efficacy of inhaled clofazimine and acetylated dextran dry powders against aerosol TB infection in mice."
Reviewers: *22, 23, AV*
A motion for approval was made and carried.
Summary: According to the World Health Organization, about 2 billion of the world's population is infected with Mycobacterium tuberculosis (Mtb); and approximately 10% of infected individuals will develop active tuberculosis (TB) at some point after infection. TB is a curable disease, yet it still has a high mortality rate (in 2016, 1.7 million people died from the disease). Clofazimine (Cfz) is a drug that has been recently added to WHO recommended list of drugs to treat drug resistant TB strains, and effectively shorten treatment times. However, oral

administration of Cfz poses problems such as severe side effects (gastrointestinal, dermal, cardiac. An existing goal to improve TB treatment consists of developing effective aerosolized delivery of drugs to directly target the lungs. Microparticle encapsulation (in the form of dry powders) of drugs has been studied for aerosol delivery of TB drugs. Dry powders with precise control over particle size for deep lung delivery can be prepared using spray drying. To address the limitations in drug release and dosage, we propose to develop polymeric acetalated dextran (Ac-Dex) encapsulating Cfz. Cfz release can be achieved through the use of pH- responsive Ac-Dex particles. Additionally, the by-products of Ac-Dex degradation (ethanol, acetone, dextran) are safe. Our specific aims include (1) developing novel Ac-Dex particles encapsulating Cfz, (2) evaluate the pharmacokinetic (PK) and efficacy studies in mice. For this study we will use C57BL/6 mice strain. The mice will be first infected with aerosol Mtb infection (H37Rv strain) and will then be treated with aerosol Cfz (dry powder and liquid) as well as intramuscular injection (Cfz solution). The pulmonary delivery will be performed using a insufflator (dry powders; Penn Century) and microsprayer (liquid; Penn Century). The treatment will be performed for two weeks (3 times/week) for a total of 6 doses. Two weeks after treatment, the mice will be sacrificed and lung and spleen Mtb burden will be evaluated. The successful completion of the above studies will demonstrate feasibility of developing Ac-Dex particles for inhaled delivery of Cfz. This research ultimately forms a platform for delivery of a variety of TB drugs and combinations thereof for TB treatment.

Sent for Pre-Review 1 on 11/21/2019.

Discussion during the meeting: The primary reviewer gave a summary of the protocol. This is a well written protocol. The PI has already responded to the review comments during the pre-review. The Biosafety Officer requested that a typo in the hazardous agent section be changed from ABSL-2 to ABSL-3. There were no other issues and the protocol was recommended for approval.

Decision: Approved: Yes=11 No=0 Abstained=0 Recused=0

200987 Breeding DMR - "FosTRAP mice for neural circuit identification in chronic pain models – Breeding Protocol."

Reviewer: *AV*

Summary: We seek to address cellular and molecular mechanisms of chronic pain and develop novel therapies for treatment. Our hypothesis is that specific neuronal cell types are activated at different time points in chronic pain models and that these cell types exhibit different electrophysiological and molecular properties compared to neurons that are not activated. This protocol supports breeding of reporter FosTRAP mice for identification of activated neurons in live slice preparations and for transfer to laboratory research protocols to support previously mentioned research goals.

Approved as a DMR by Attending Vet on 11/8/2019.

200995 Breeding DMR - "Mouse Models of Pancreatic Cancer."

Reviewer: *AV*

Summary: This is the breeding protocol for our experimental protocol. No procedures on the breeding protocol. Two mouse models will be used in the experimental study, and the procedures include breeding, cancer cell injection, observation (touching and ultrasound), transport, and gene KO. NOC-SCID IL2 receptor gamma chain knockout (NSG) mice will be used as acceptors for pancreatic cancer cell injection. This experiment monitors tumor formation

and growth in immune system deficient mice (NSG). The other model is Ptf1acre/+, LSL-KrasG12D/+, Tgfbr2flox/flox mice (Tgfbr2 KO), which develop pancreatic cancer at age 4 weeks. The interested gene will be KO at Tgfbr2 KO background to determine if the process of pancreatic cancer development is affected. This study will illustrate role of the interested gene in pancreatic cancer development, which could be potential target for anti-cancer purpose.
Returned for modification on 12/5/2019.

Item # 5 Major Amendments:

200423 - "Study of papillomavirus entry and infection in mouse models."
Reviewers: *17, 26, AV*
A motion for approval for DMR was made and carried.
Summary: We would like to investigate if MEK inhibitors, Trametinib and Cobimetinib (FDA approved compounds in humans), have antipapillomavirus properties. This will require inoculating mice with mouse papillomavirus putting them into different treatment groups and tracking the tumor growth over time. An additional 48 mice will be needed to carry out this work.
Returned for modification on 12/2/2019.
Discussion during the meeting: The Chair gave a brief summary of the protocol amendment. There were no PI responses yet for this amendment so the protocol was voted for approval as a DMR. The reviewers will remain the same per the IACUC Chair.
Decision: Approval for DMR: Yes=11 No=0 Abstained=0 Recused=0

200640 - "A Novel Advanced Resuscitation Fluid for a Rat Model of Traumatic Brain Injury with Hemorrhagic Shock".
Reviewers: *22, 26, AV*
Summary: Change in PI because the existing PI is leaving UNM.
Approved as a DMR by Sub-Committee on 11/25/19.

200717 DMR - "A mouse model of Mycobacterium abscessus lung infection that mimics human infection."
Reviewers: *18, 23, AV*
Summary: For our upcoming experiment we propose experimental groups for both Cre (-) and Cre (+) post-tamoxifen-treated mice in which the mice receive anti-mouse Ly6G to deplete neutrophils. These mice will receive 1.0 mg of anti-mouse Ly6G antibody i.p. 24 hours prior to infection. This amount of antibody has been shown to result in marked depletion of neutrophils for up to 72 hours (1). Post-infection, the mice will be closely monitored (twice daily) for signs of acute infection including coughing and sneezing, unkempt erect coat, discharge from the eyes, nose, urinary or genital organs, decreased movement, constant scratching, lack of balance, and stumbling or stiff legged gait. If mice exhibit these signs they will be euthanized. If mice appear to be tolerating the effect of anti-mouse Ly6G antibody treatment with no adverse signs of acute infection, they will undergo a second i.p. injection of anti-mouse Ly6G antibody 2 days post-infection, again followed by twice a day monitoring in the 72 hours post injection period.
Approved as a DMR by Sub-Committee on 11/15/2019.

200751 - "Brain stimulation in the mouse model of recovery from acute brain injury."

Reviewers: *18, 27, AV*
Summary: Change in PI because the existing PI is leaving UNM.
Approved as a DMR by Sub-Committee on 11/25/2019.

200767 - "Treatment of the rat malignant brain tumor".
Reviewers: *11, 8, AV*
Summary: Change in PI because the existing PI is leaving UNM.
Approved as a DMR by Sub-Committee on 12/2/19.

200902 DRPs) for prevention of leukemia metastasis.".
Reviewers: *20, 24, AV*
Summary: Change in PI because the existing PI is leaving UNM.
Approved as a DMR by Sub-Committee on 11/25/19.

200921 - "The effect of pulsed electromagnetic field on synaptic transmission and calcium signaling in rat hippocampal slices".
Reviewers: *12, 25, AV*
Summary: Change in PI because the existing PI is leaving UNM.
Approved as a DMR by Sub-Committee on 11/26/19.

Item # 6 Minor Amendments:

200600 - "Non-invasive Imaging and Irradiation Optimization by the Animal Models Shared Resource."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 11/21/2019.

200653 - "A Mouse Model for Mechanisms of Immune Dysregulation Produced by Uranium, Arsenic, and Metal Mixtures (Biomedical Project (BP2), Superfund Center)."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 11/20/2019.

200734 - "A Rat Model for Microsurgery Training."
Reviewer: *Chair*
Summary: Add/remove staff
Approved administratively per IACUC Chair on 11/8/2019.

200765 - "Breeding Protocol for Cancer Center Core Support."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved administratively per IACUC Chair on 11/20/2019.

200806 Breeding - "Mouse Models of Obesity and Diabetes."
Reviewer: *AV*

Summary: 1.We are going to generate UCP1-CRE JUNB KO by cross JUNB flox(n=3) mice with UCP1-CRE(n=1)(from Jackson lab).
2. We are going to generate adiponectin transgenic animal model by using BL6 mice cross with delta-gly adiponectin mice (from UTSouthwestern Phillip Scherer Lab).
3. We are going to generate Raptor ko or Raptor/ATG7 dko inducible animal model by using Raptor flox or Raptor/ATG7 dflox cross with adipoP-rtTA x TRE-Cre mice (from UTSouthwestern Phillip Scherer Lab).
Approved by Attending Vet on 11/14/2019.

200831 - "Mouse Breeding protocol for Immunity and Inflammation Mechanisms."
Reviewer: *AV*
Summary: To recover 129-CisfxLyz2-Cre strain, we request to add 2 B6.LysMCre (Lyz2-Cre). Net change: +2.
Approved by Attending Vet on 11/11/2019.

200884 - "Breeding protocol for ovarian cancer mouse models."
Reviewer: *AV*
Summary: With this amendment, we plan to add a new transgenic strain (B6.Cg-Foxp3tm2Tch/J; Foxp3-eGFP; https://www.jax.org/strain/006772) to our breeding colonies. This strain was developed to mark the regulatory T cell subsets by the co-expression of green fluorescent protein under the endogenous promoter of Foxp3 molecule (regulatory T cell-specific transcription factor). As reported in the original paper (Haribhai D. 2007 https://www.jimmunol.org/content/178/5/2961.long), GFP expression was only seen in Foxp3+ regulatory T cell subsets. This strain has been used broadly in the studies about regulatory T cells. To start the experiments about the regulatory T cells subset in our ovarian cancer mouse models (19-200823-HSC), we will obtain initial breeders from Jackson lab and set up a colony at UNM ARF to obtain enough number of mice without excessive cost.
Approved by Attending Vet on 11/14/2019.

200960 - "Mouse Breeding Protocol - Cargo Of Exosomes and Microvesicles In Tuberous Sclerosis Complex."
Reviewer: *AV*
Summary: Additional mouse strains have been imported to our colony. These strains were not previously included in the breeding protocol. The breeding design table has been updated to reflect this. It will increase our animal usage total from 115836 to 121884.
Approved by Attending Vet on 10/31/2019.

200973 - "Spreading Depolarizations and Post-Ischemic Injury in Mice."
Reviewer: *Chair*
Summary: Add/remove staff.
In administrative review.

Item # 7 Annual Renewals:

200602 DMR - "Mechanisms of Breast Cancer Tumorigenesis and Metastasis"
Reviewer: *Chair*

Species: Mouse
Approved as a DMR by IACUC Chair on 11/11/2019.

200652 Closure - "A rat model of Diabetic Ketoacidosis (DKA) for microneedle-extraction and analysis of interstitial fluid."
Reviewer: *Chair*
Summary: Over the past year we have continued to identify ketone levels in interstitial fluid of CD Hairless rats. We have used 21 CD Hairless rats to date. We faced ongoing challenges with STZ not inducing DKA or increased blood ketones in the CD Hairless rat strain. It was known that STZ effects are species-dependent however, no one had tried this in CD Hairless rats prior. We found that doses of 65 mg/kg did not result in signs of diabetes. Doses of 100 mg/kg and above were typically lethal. Doses in between 65 and 100 mg/kg produced unreliable illness or no illness at all. However, with control rats (no STZ injection) we had an important discovery due to this project. Although blood ketones are 0.0 mM in healthy control rats, ketones that reliably average around 0.3 mM were found in the interstitial fluid (ISF) of all these control rats. This is, to our knowledge, the first measurements of ketones in ISF and the first comparison of that with blood ketones. This could be very important for our future development of ISF ketone sensors/patches. Since the STZ injections were not working to elevate ISF or blood ketones, we chose to look at rats that went through the approved overnight fasting prior to STZ injection, but we did not inject STZ after the fasting. We extracted ISF from these fasted (non-injected) rats and have found that ketones in ISF rise correspondingly with length of fasting. This would be expected, but the interesting findings have been that the Fasting ISF ketone levels rise much higher than that of the blood and show more dynamic changes. We believe simply looking at fasting rats will prove more beneficial that any continued attempts at STZ injections. We found that ketones increased with a short fasting and could be measured in the ISF. We are currently working on a manuscript with results. This completed our funded study and we now wish to close the protocol.
Closed administratively per IACUC Chair on 11/4/2019.

200654 DMR - "Breakthrough Threshold of Intracranial Pressure Autoregulation"
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/11/2019.

200658 with Minor DMR - "Trafficking of nanoparticles and synthetic RBC in murine breast and ovarian tumors."
Reviewer: *Chair*
Summary: Add/remove staff.
Approved as a DMR by IACUC Chair on 11/14/2019.

200666 with Minor DMR - "Prenatal Alcohol Exposure and Corticostriatal Control of Behavioral Flexibility ".
Reviewers: *Chair, AV*
Summary: We have made good progress on Project 1 to investigate the effects of optogenetic stimulation on deficits in behavioral flexibility seen after PAE. In response to reviewers, we are requesting the addition of Venus-VGAT mice to confirm efficacy of the AAV-ChR2 for excitatory glutatmatergic cells. Briefly, Venus-VGAT mice (age 5-6 weeks) will receive surgery

to transfuse AAV-ChR2 or AAV-mCherry bilaterally into the lateral orbitals. At around age 9-10 weeks, mice will be sacrificed and brains will be sliced (300µm) for ex vivo electrophysiology, during which a blue light laser will be shined on fluorescence-expressing cells.
We are requesting 30 mice (15 per trt) to perform these control experiments.
Approved as a DMR by IACUC Chair and Attending Vet on 11/12/2019.

200671 DMR - "Acquired Post-Hemorrhagic Hydrocephalus from Intraventricular Hemorrhage in Rats."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/11/2019.

200686 Closure – "Investigation of Microspheres Distribution in Rats Using PET imaging."
Reviewer: *Chair*
Species: Rat
Summary: The research that I did using the protocol established that F-18 labeled hydroxyapatite microspheres were stable in vivo. This was very important property that could only be proven in an animal. This experiment established that the F-18 did not disassociate from the microsphere. Thus, I was able to show that the F-18 labelled microspheres can be used as surrogates for Y-90 therapeutic microspheres. The F-18 PET data can be used to determine radiation dose and treatment planning. At this time, moving forward with research in this area is not a top priority. Future investigations in this area will likely be done by other investigators.
Closed administratively per IACUC Chair on 11/14/2019.

200748 DMR - "Deficient response inhibition and parietal cortex alterations after prenatal alcohol exposure in the mouse".
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/12/2019.

200749 Closure - "Mouse breeding for studies of NMDAR mediation of executive control ".
Reviewer: *Chair*
Closed administratively per IACUC Chair on 11/5/2019.

200751 DMR - "Brain stimulation in the mouse model of recovery from acute brain injury."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/20/2019.

200756 Closure - "Vascular benefits of omega-3 polyunsaturated fatty acids in mice."
Reviewer: *Chair*
Closed administratively per IACUC Chair on 11/4/2019.

200764 DMR - "Mouse dendritic cell subsets in filovirus vaccination."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/8/2019.

200765 DMR - "Breeding Protocol for Cancer Center Core Support."
Reviewer: *AV*

Approved as a DMR by Attending Vet on 11/11/2019.

200771 DMR - "Assessment of the immune responses induced by VLP-based vaccines against infectious diseases in mice."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/8/2019.

200772 DMR - "Novel therapies to target ovarian cancer in a mouse model of peritoneal metastasis."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/11/2019.

200774 Tissue - "Post-Mortem Magnetic Resonance Imaging of Tissue Samples of Various Species".
Reviewer: *Chair, AV*
Species: Animal Tissue
Approved by IACUC Chair and Attending Vet on 12/3/19.

200777 Breeding DMR by Vet - "Breeding Protocols for Mouse Models of Brain Injury and Repair".
Reviewer: *AV*
Approved as a DMR by Attending Vet on 11/25/19.

200781 DMR - "Epigenetic changes in mouse brain following prenatal neurotoxic exposures."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/8/2019.

200782 DMR - "Breeding of Acid Sensing Ion Channel Null Mice."
Reviewer: *AV*
Approved as a DMR by Attending Vet on 11/14/2019.

200783 Closure - "Characterization of Microneedle Interstitial Fluid Extraction in CD Hairless Rats."
Reviewer: *Chair*
Summary: This project did not end up getting funded and therefore work was not initiated. We now wish to close this protocol.
Closed administratively per IACUC Chair on 11/4/2019.

200784 DMR - "Using In vivo model of mice and rats to study Mechanisms of Increased Vascular Permeability in Diabetic Retinopathy."
Reviewer: *Chair*
Approved as a DMR by IACUC Chair on 11/11/2019.

200786 with Minor DMR - "Mouse Breeding and holding protocol."
Reviewer: *AV*

Summary: The CCL2 fl/fl mice will be crossed with Cre-CamkII mice to obtain COX2 floxed Cre+ KO mice. CCL2 floxed Cre+ KO male mice will be used for MCAO after 3 months of age. B6-CCL2:CamK2aCre fl/fl Cre mice will be used to knockdown CCL2 (MCP1) specifically in neurons. This will allow us to study the role of MCP1, a pro inflammatory molecule, in neurons of these mice. Since MCP1 are made from multiple different cell types in the body this is the way to study the role of MCP1 particularly in neurons.
Approved as a DMR by Attending Vet on 11/20/2019.

200787 with Minor DMR - "Molecular basis of hyperhomocysteinemia induced brain injury."
Reviewers: *Chair, AV*
Summary: The COX2 floxed Cam2aCre+ mice that is being generated will be used to evaluate the role of neuronal release of PGE2 in inducing inflammatory response in the ischemic brain under hyperhomocysteinemic brain. COX2 is the rate limiting enzyme in the PGE2 synthesis pathway. We are proposing an increase in 88 COX2 floxed Cam2aCre+ mice for this purpose.
Approved as a DMR by IACUC Chair and Attending Vet on 11/20/2019.

200788 with Minor DMR - "Breeding Protocol - Mouse Models of Development & Cancer".
Reviewer: *AV*
Summary: Add/remove staff.
Approved as a DMR by Attending Vet on 11/11/2019.

200797 with Minor DMR- "Breeding protocol for Molecular Regulation of T cell migration."
Reviewer: *AV*
Summary: Add/remove staff.
Approved as a DMR by Attending Vet on 11/8/2019.

200816 Breeding DMR - "Mouse Breeding Protocol for Arsenite-enhanced Skin Carcinogenesis by UV Radiation".
Reviewer: *AV*
Approved as a DMR by Attending Vet on 11/11/2019.

General Business:

1) USDA Annual Reports were submitted online.
2) USDA Registration Renewals were submitted.
3) Discussion of consolidation of protocols for one PI – A PI who is a working retiree (25% effort) is now planning to manage 10 protocols. Five protocols from another PI who just switched from full time to adjunct professor were just transferred to this PI. Options were discussed by the committee. However, due to lack of information, the committee agreed that a subcommittee should meet with the new PI and adjunct Co-I before making final decisions on administration and oversight of these protocols.
4) There was a discussion about the new Pulse VPN option. Citrix is still available.
5) IPRA Update – The AV and the OACC Operations Manager gave an update on the latest IPRA request from NEAVS.

The meeting was adjourned at 1:08 PM.
Respectfully submitted by the Recording Secretary_____