I. Summary and Significance.

Stroke kills more women today than breast cancer and AIDS combined and unfortunately none of the available clinical treatments are very effective. While the incidence of stroke is generally higher in men, women are more severely affected than men with reduced recovery, greater recurrence (1,2) and increased mortality, accounting for over 60% of stroke-related deaths (1). Experimental and clinical data suggest that sex differences in stroke risk and outcome may be due to sex hormones (e.g. estrogen, progesterone) (2). Furthermore, post-menopausal women have increased stroke severity, which is further exacerbated by advanced age (3). These findings suggest that age and gender are important and female sex hormones may be protecting younger women from stroke. Although gender differences are known to influence stroke outcomes, male animal models are often exclusively used to test new stroke therapies, rather than models with both genders. As such, our current understanding of stroke in women is exceedingly limited and would benefit from experimental models relevant to women. As a model organism, the rhesus macaque (Macaca mulatta) is often chosen as it represents the most widely used and relevant models for studying human aging and disease. Our lab developed the first male rhesus macaque cortical stroke model, which demonstrates similar clinical outcomes as humans after stroke, including systemic inflammation, infiltration of the brain by inflammatory cells, functional deficits including weakness or paralysis of the limbs and face, and reduced physical activity (5). We propose to transfer our experience to an aged female monkey to address their susceptibility to ischemia in the brain.

Gender differences evoke questions on sex hormones, such as estrogen, which target the reproductive, cardiovascular, skeletal, immune and nervous system, but also play a role in inflammation and disease (3). Hence, estrogen is thought to particularly influence diseases that increase as a function of age, such as stroke. Estradiol (E2) has many direct effects on the brain, starting during development and influencing plasticity in adults. These central estrogen effects can take place in a matter of minutes via membrane receptors, within hours for gene regulation via transcriptional factors (4) and effect anatomical changes shortly thereafter (5). All of these functions can be modulated by the action of endogenous estrogens as well as by various synthetic forms prescribed to aging women. With stroke, estrogen administration is protective in rodent experimental models, capable of reducing damage in more sensitive, aged rodents (2). Paradoxically, clinical studies in post-menopausal women given estrogen therapy (ERT) showed exacerbated stroke-associated mortality and no reduced risk of stroke compared to women not given ERT. However, ERT was provided belatedly in those clinical studies, and it has been postulated that the protective effects of estrogen may be enhanced only when initiated soon after menopause.

We have preliminary data (below) in surgically-menopausal, young adult, female rhesus monkeys that show less ischemic damage to the brain than their intact male counterparts. Although there are many interpretations of this outcome, with regards to the female animals, there are similar outcomes in other studies that reveal resilience in young adult animals that have been ovariectomized (OVX) to lower sex hormone levels. For example, cognitive function improved with ERT in OVX, aged female rhesus versus those receiving only placebo (5). However, young OVX adults in the same study, on either placebo or ERT, performed equally as well as the OVX aged females on ERT. Hence, young adult females appear protected from the negative effects of estrogen loss after OVX, whereas older adults are not, although supplemental E2 can improve cognition in aged females. We show similar data (Fig 1A), indicating positive E2 effects on a cognitive task in OVX aged adult females, using the same E2 replacement paradigm outlined in this proposal. Overall, the findings in female rhesus macaques suggest that estrogens are important primarily in older females.

What could account for this difference in performance between old and young female monkeys lacking estrogens? We postulate the answer may lie in the neurosteroid synthesis pathway, an endogenous biosynthetic pathway that allows estrogens to be produced locally in the brain. Of interest, a precursor of this brain pathway is the adrenal steroid DHEA (Fig 1B), a product that declines precipitously with age in men and women. Thus, old female animals gradually lose two potential sources of E2 upon aging, one produced by the ovaries and another produced by the brain itself via pathways involving DHEA (Fig 1C). Therefore, another hypothesis is that while young OVX animals lose ovarian estrogens, they still have high DHEA levels and can synthesize E2 in the brain, sparing estrogen-dependent function. This system may explain our preliminary stroke results in female macaques. We show here that young adult females are still protected from stroke after OVX when compared to age-matched males (Fig 2), further suggesting a role for another source of estrogen (eg. brain neurosteroid synthesis) or nonhormone-related effects (eg. genetics) specific to young adults.

Proposal Title: Modeling stroke in the female nonhuman primate to evaluate gender differences.
II. Methods (brief outline)

Our study will examine stroke outcome following menopause in aged female monkeys given estrogen replacement therapy in the form of endogenous Estradiol (Estradiol/17-beta, E2) or placebo. Approximately 1 week following the disappearance of hormones from the systemic circulation, magnetic resonance imaging (MRI) will be performed to examine the status of the brain before treatment and stroke. Animals will then be given implants containing E2 or placebo (n=5/group). Two months later MRI will be performed prior to the stroke using our published protocols and 2 days after stroke MRI will again be evaluated (7). Imaging of inflammatory cells will be performed at this time using dynamic susceptibility contrast (DSC) MRI. Changes in brain infarct severity will be determined using MRI scans 2 days after stroke. We will observe animals daily after stroke for clinical condition and neurological function. Accelerometers devices that measure physical activity will be worn for the duration of the study by all animals to identify any changes in physical activity following stroke that may be due to E2 or gender. Immunity also typically wanes in aging women causing increases in chronic infection, whereas ERT is known to increase immune function. Thus we will also examine systemic immune status (e.g. blood cell distribution and phenotype, plasma cytokines and chemokines) in all animals prior to and following stroke (+/-E2) to evaluate changes due to gender or estrogen. Additionally, within hours to days of injury circulating inflammatory cells infiltrate potentially salvageable tissue in the ischemic brain contributing to secondary damage and cell death (9). Ferumoxytol is an ultra-small supra-paramagnetic ironoxide nanoparticle known to be taken up by phagocytic cells (e.g. macrophages, reactive astrocytes, activated microglia involved in brain injury due to ischemia (8)). Studies show that infiltrating cells can be detected in the brains of rodents, monkeys and humans using delayed imaging 1-2 days following ferumoxytol infusion and stroke initiation (Fig 2). This feature of ferumoxytol provides a unique opportunity to noninvasively examine inflammatory processes associated with these cells. We will also measure ferumoxytol uptake in the brain before and after 60 days of E2 treatment, as well as 2 days following stroke. Lastly, we will examine cerebral blood flow and volume (CBF, CBV) using advanced MRI protocols. These factors are altered during menopause, stroke, and with hormone therapy and any changes observed are likely to contribute to stroke outcome. Necropsy will be performed 2 days following stroke after blood collection and MRI and brain tissue will be obtained for histopathology. Lymph nodes, blood cells, blood plasma, and spleen will be preserved for immune profiling. Cerebral spinal fluid will also be collected and examined for inflammatory mediators.
III. Outcomes

Due to gender differences, it appears likely that men and women may require different treatments to achieve optimal clinical benefit, yet no gender-specific stroke treatments exist. The fact that potential stroke therapies are almost exclusively tested in stroke models using males could mean that few, if any, effective treatments optimized for women suffering stroke will be discovered unless we act to improve our understanding of stroke in women. Studies using this newly developed model will have significant impact on our understanding of age, gender, and hormone replacement in stroke. Additionally, aging is associated with dysregulation in immune function, a condition referred to as “immune senescence”. Thus immunity is a feature of general interest and one highly applicable to stroke as circulation immune cells infiltrate the CNS and contribute to the damage observed in the brain. Knowledge will be gained in all of these areas leading to understanding of human stroke, and potentially predictive biomarkers and novel treatments for stroke. This model will also facilitate the testing of future treatments relevant to women in stroke. Upon completion this proposal, future grant applications will employ this model to evaluate the relationship between the duration of hormone deprivation and stroke outcome. Future studies will examine the impact of other medications given to women on stroke risk or outcome. Additionally, by evaluating differences in the female response to stroke (e.g. brain response, blood cell response, brain and systemic inflammatory response), we could identify optimal targets for stroke therapy in women. As we have done in mouse stroke models, our lab intends to systematically characterize the genomic, proteomic, and metabolic changes that occur following stroke in this female model as compared to males. The differences found can then be leveraged to optimize new therapeutic strategies for women at risk or those suffering from stroke. These represent only a fraction of the important questions that can be addressed using this unique stroke model, many of which can be addressed using tissues and samples obtained from the studies proposed here. As our current grant funding does not support the studies proposed in this application, funding through the Circle of Giving will represent a critical step toward future funding opportunities aimed at better understanding stroke in women through experimental modeling in primates.

Leveraging Existing Grants. Our current grant funding does not support these studies; however our existing grant does support stroke studies in adult female OVX animals and adult males. Importantly, all of these data can be combined to examine age and sex-related differences, further leveraging the resources provided by our existing grants. These combined efforts will establish the basis for a female primate stroke model that could subsequently be leveraged to obtain additional funding from other sources (eg. Hazel K. Goddess Fund, American Heart Association, National Institutes of Health).
IV. Budget
All funds awarded for this application will be used to cover the cost of animals, surgery, treatments, MRI, and the required animal husbandry. No funds will be used for salaries or any expenses not listed below in Table 1.

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V. Research Appendix  
a. Specific aims  
We propose to examine stroke in aged female rhesus macaques in order to gain a practical understanding of how gender and age can affect stroke outcome. Also, since hormone replacement therapy is a common treatment for aging women and recent data suggests uncertain risks may be associated with hormone replacement therapy, we propose to examine stroke outcome following menopause in aged female monkeys given estrogen replacement or placebo. These results will determine whether ERT is detrimental or protective when supplied soon after hormone deprivation in aged females, representative of post-menopausal women. Importantly, hormone deprivation, aging, immunity, and hormone therapy reflect clinical conditions that have high relevance to women and stroke and all of these can be investigated using this experimental model. Therefore, we propose the following specific aims:  
Aim 1) Evaluate the effect of the loss of endogenous sex hormones on stroke outcome in aged females, a population of animals that model post-menopausal women. 
Aim 2) Examine the effect of estrogen replacement on stroke outcome and immunity in aged female monkeys, a study that models the clinical scenario facing post-menopausal women.

b. Preliminary studies  
A risk factor specific to women with natural menopause before 42 years of age is that they have twice the stroke risk of all other women in different age groups [4], stressing the potential serious contribution of estrogen deprivation to stroke risk and outcome. To model this high-risk adult female post-menopausal population, we ovariectomized adult rhesus macaque females prior to stroke. Using identical methods our preliminary studies evaluated gender differences comparing adult males to female monkeys undergoing surgically induced menopause (ovariectomized, OVX). Animals were given a stroke ~2-3 months following OVX surgery. This initial study showed a statistically significant reduction in stroke outcome in female (OVX) versus male rhesus macaques (Fig 3). Thus under conditions that mimic menopause, adult female monkeys are still protected relative to their male counterparts of similar age and demographics. We postulated that while circulating hormone levels were confirmed to be absent at the time of stroke in female monkeys used in our study, the activity of the neurosteroid hormone pathway in the brain could have provided neuroprotection to adult OVX females. In contrast, hormone deprivation in adult mice resulted in substantial worsening of stroke symptoms to a level similar to that of males suggesting species differences also exist. We concluded that substantial gender differences exist between stroke outcome in adult male and female monkeys and these dimorphisms may involve brain-derived estrogen or other non-hormone factors that cannot be modeled adequately in rodents. Thus we hypothesize that estrogen synthesis is reduced in the aged due to decreased DHEA and thus stroke outcomes will be more severe in aged females lacking both sources of estrogens, whereas exogenous treatment with E2 will offer protection similar to the results shown for adult OVX females (Fig 1). This initial experiment suggested that both hormone-related and unrelated effects impact stroke in female monkeys compared to males. These significant findings warrant further investigation.

c. Research Design and Methods  
Aim 1) Evaluate the effect of loss of endogenous hormones on stroke outcome in aged females, a population of animals that model post-menopausal women. Studies have provided substantial support for the idea that estrogen can play a protective role in stroke and loss of estrogen is detrimental. Clinical and experimental findings suggest that the length of time a female is without hormones correlates with worse stroke incidence and outcome, a hypothesis testable in this model. We hypothesize that estrogen loss in aged animals will be detrimental causing a more severe outcome compared to adult OVX females tested in our...
previous study (Fig. 3). Immune function will be compromised in aged females and thus infiltrates in the brain will be increased compared to young adult females.

<table>
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<td>Hormone therapy</td>
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Aim 2) Examine the effect of estrogen replacement on stroke outcome and immunity in aged female monkeys, a study that models a clinical scenario relevant to postmenopausal women. We hypothesize that the timing of estrogen therapy with respect menopause may determine if treatment is beneficial or detrimental. In parallel with Aim 1, OVX animals will be randomly assigned to receive physiological levels of estradiol or placebo (Aim 1) for 60 days via subdermal implant. Stroke will then be performed as described in Aim 1. Methods. To test our hypotheses we will ovariectomize aged females to induce a state of hormone deprivation (menopause) and one-week later supplement half of the animals with E2 for 2 months prior to stroke and other with placebo (Table 2). We will evaluate the extent of stroke, as we have previously published (7, 8, 10-13). In a blinded efficacy study we showed that the male ischemic brain can be protected with our novel therapeutics (7) as reflected by measured variables (Table 3). Measures (Table 3) will be taken at: 1) baseline after OVX just prior to E2 treatment initiation, 2) following 60 days of E2 treatment immediately before stroke, and 3) two days after stroke. MR imaging. We previously implemented anatomical and dynamic susceptibility contrast (DSC) to quantify the extent of infarction and changes in cerebral blood flow (CBF) during and after cerebral ischemic injury in this model (13). A T2- weighted turbospin echo scan, TE=56/TR=5280 using a 256x256 matrix over a 128x128 FOV, with 50, 1mm axial slices will be collected (infarct size scan). T1- weighted MPRAGE, TE=3.74/TR=2500 using a 256x256 matrix over a 153x153 FOV, 50, 0.6mm axial slices collected (anatomical). A DW scan, TE1=75/TE2/TR=6441 using a 96x96 matrix over a 144x144 FOV, 40, 1.5mm axial slices will be collected (diffusion scan). DSC MRI and Associated Measurements: A 2D multislice T1-weighted turbo-spin echo sequence (TSE; TE13/TR=2500) using a 192x256 matrix over a 128mm x 128mm FOV with 66 1mm axial slices will be collected before contrast administration. A 2D multislice T2* gradient recalled echo sequence (GRE; TE12/TR1000/FA45) will be collected using a 256x256 matrix over a 96mm x 128mm FOV with 66 1mm axial slices. Dynamic susceptibility contrast (DSC) MRI data will be acquired to estimate regional cerebral perfusion in the rhesus macaque. A T2*-weighted time series scan will be collected using a 2D multislice gradient recalled echo EPI sequence (TE13/TR=1500) oriented in the axial plane with a (128mm)2 field of view encoded using a (128)2 matrix and a total of 30 near contiguous 1mm sequential slices collected. The slice pack will be centered to provide complete coverage of the infarct. A bolus injection of ferumoxytol (IV; 15mg Fe/ml) totaling 4 mg/kg Fe will be chased with 5 ml normal saline. The T2*-weighted images will be collected for 150s (100 volumes). Ferumoxytol will be injected after a baseline collection of 15 image volumes (22.5 s). The 2D T1-weighted TSE and 2D T2*-weighted GRE sequences (see above) will be repeated immediately post-ferumoxytol injection to estimate tissue blood volume at high spatial resolution [(T2*-weighted post-ferumoxytol)-[(T2*-weighted pre-ferumoxytol)]] and then again 48hr later for tissue Fe uptake (macrophage imaging).

Immunity. Ferumoxytol has been implemented in Neurosurgery at OHSU as part of a clinical trial (fig 2 and Trial ID: NCT00660543 at www.clinicaltrials.gov), as well as at our primate center in Japanese macaques. We propose to similarly quantitate infiltrates in our stroke studies using delayed ferumoxytol imaging. In rhesus macaques, specific immune cell populations are conserved in younger animals compared to older, with decreased pathogen recognition receptor expression and activity of immune cells (e.g. phagocytosis), and a shift toward regulatory circulating cytokines (e.g. IL1Ra) being observed upon aging, similar to changes in humans. Thus, we will evaluate changes in immune cell distribution / phenotype by flow cytometric analysis, and plasma cytokines, providing information about age and gender-related changes in immunity due to stroke.

d. References
NAME
Frances Rena Bahjat, Ph.D.

POSITION TITLE
Research Assistant Professor

eRA COMMONS USER NAME (credential, e.g., agency login)

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

<table>
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<th>INSTITUTION AND LOCATION</th>
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<td>Benedictine University, Lisle, IL</td>
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<td>University of Florida College of Medicine, Gainesville, FL</td>
<td>Ph.D.</td>
<td>2002</td>
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A. Personal Statement
For over 3 years I have been involved in the evaluation of neuroprotective agents in the proposed nonhuman primate model of stroke in male animals in collaboration with Drs. Mary Stenzel-Poore and Steven Kohama. This effort has afforded me the opportunity to gain significant knowledge and experience with stroke modeling in mice and monkeys. For the 8 years prior to that, I was pursuing research in a corporate drug discovery and development environment, primarily functioning as an in vivo biologist and preclinical drug development specialist in the areas of inflammation and autoimmunity. As a research scientist at several pharmaceutical companies, I have experienced drug development from the hit stage to clinical trials and have strong interest in developing therapeutics for diseases with high medical need. During my career in industry, I participated in the discovery and development of therapeutics directed at many different targets (ex: inhibitors of TNF, IL-1, NF B, Syk kinase, Aurora kinase, JAK3, JAK2, PKCtheta, and proteasome inhibitors). My last position was the director of pharmacology where I was overseeing all in vivo efficacy, PK and drug tolerability studies as well as clinical assay development. While I have a strong immunology background with a specific emphasis on inflammation biology, I have also participated heavily in the preclinical development of therapeutics targeting diseases affecting the brain, such as multiple sclerosis, using murine models of EAE (experimental autoimmune encephalomyelitis). My experience includes assembling preclinical IND-enabling study packages containing data from tolerability, PK/PD, efficacy and mechanism of action studies in various species, as well as biomarker discovery and clinical monitoring. I have played an instrumental role in four IND submissions resulting in human clinical trials in oncology and autoimmunity indications. These skills make me uniquely qualified to participate in this model characterization study designed to identify the next generation of stroke therapies for women.

B. Positions and Honors

**Positions and Employment**

1996-1997 Teaching and Research Assistant, Benedictine University, Lisle, IL
1997-1998 Research Technician, University of Florida College of Medicine, Gainesville, FL
1998-2002 Doctoral Candidate, University of Florida College of Medicine, Gainesville, FL
2002-2004 Research Scientist II, Neureus Pharmaceuticals, San Diego, CA
2004 Scientific Consultant, Inflammation and Autoimmunity Preclinical Drug Development Specialist, Neureus Pharmaceuticals, San Diego, CA
2005-2008 Associate Director, Pharmacology Research & Development, Rigel Pharmaceuticals Inc., South San Francisco, CA
2009- Research Assistant Professor, Oregon Health and Sciences University, Portland, OR
Honors and Awards

1994    Freshman Chemistry Award, Indiana University
1995-1997    Award for Excellence in the field of Biology, Benedictine University, all semesters
1995-1997    St. Benedict Award and Academic Scholarship for academic achievements, Benedictine University, all semesters
1995-1997    Dean’s list, Benedictine University, all semesters
2000-2001    NIH Fellowship, T32 NIH Training Grant, Department of Rheumatology, University of Florida College of Medicine, Gainesville, Florida

Professional Organizations and Committees

2001-2002    President and Past President, College of Medicine Graduate Student Organization, University of Florida College of Medicine, Gainesville, Florida
2001-2002    Chairman of College of Medicine Career Development Committee, University of Florida College of Medicine, Gainesville, Florida
2001-2002    Director of Alternative Careers in Science Seminar, University of Florida College of Medicine, University of Florida College of Medicine, Gainesville, Florida

Member, American Association of Immunologists

C. Selected Peer-reviewed Publications


8. Ta-Hsiang Chao, Thanh Lam, Binh G. Vong, Paqui G. Traves,[Sonsoles Hortelano, Chinmay Chowdhury, F. R. Bahjat, G. Kenneth Lloyd, Lyle L. Moldawer, Lisardo Bosca, Michael A. Palladino, and Emmanuel A.


D. Research Support

Ongoing Research Support

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NIH/NINDS

Development of Toll-like Receptor Agonists as Neuroprotectants in Brain Ischemia

The goal of this application is to develop TLR agonists as neuroprotectants in a preclinical model of nonhuman primate stroke. Studies will address optimal dosing and time windows for candidate molecules, as well as gender and age effects on stroke outcome.

Role: Co-Investigator
A. Personal Statement

Dr. Kohama is head of the Primate Aging Resource (PAR), which oversees the management and usage of aged non-human primates at the Oregon National Primate Research Center (ONPRC). The aged animal resource, identified as the Primate Aging Study (PAS) enjoys NIA support for the housing and maintenance of Indian-origin rhesus macaques, making an aging colony plausible. Dr. Kohama’s training is diverse and includes the fields of neurobiology, neuroendocrinology and aging, which occurred during his Ph.D. training at U.S.C. in the Andrus Gerontology Center. He has conducted macaque-based work over the past 20 years at ONPRC, including studies on behavior, physiology, histology, neuropathology and transcriptome analysis of aging and hormonal effects in the brain. Currently he is a Senior Staff Scientist in the Division of Neuroscience at ONPRC, as well as a Scientific Director for the American Society of Aging Research (AGE) and an Adjunct Scientist to the MRI-based, Advanced Imaging Research Center at OHSU. With the latter appointment, tools were created for measurement of peripheral fat (MRS) and volumetric analysis of the CNS. Other areas of aging research that use the aged nonhuman primate model include, exploring the effects of aging on the neuroendocrine axis, efficacy of hormone replacement paradigms on cognition in males and females, the effect of innate immunity manipulation for minimizing ischemia (stroke) damage, the exploration of immune senescence, viral reactivation and the examination of white matter perturbations in the brain. The most recent initiative is a new study that will explore the interaction of diet and both immediate and delayed estrogen replacement in aged females. This will be a multidisciplinary, multi-investigator approach, which will examine treatment outcomes on metabolism, bone, cognition, cardiovascular and other endpoints of interest.

The current proposal will extend the macaque cortical stroke model into older female, rhesus macaques. This is an ideal use of the model as it reproduces the cortical complexity, reproductive physiology and longevity of women much better than other lower vertebrates. In addition, scientists at ONPRC have been manipulating the reproductive axis in female rhesus for many years, especially in the field of hormone-replacement therapy. A huge advantage of the current application is that this grant will leverage an existing U01 that has focused primarily on young male animals. From the standpoint of developing the macaque cortical stroke model, that has been a tremendous success and will provide a platform for comparison of outcomes with the current application. However, from the standpoint of understanding the issue of gender and aging, conditions of fundamental importance for understanding the mechanisms of spontaneous ischemic damage in the central nervous system in humans, these additional studies are required to fulfill a complete translational model. To facilitate this process PAR will provide an active interface between investigators and the Division of Comparative Medicine, providing expertise for identifying specific animals for the proposed study and assisting in the management of this study. The development of novel, additional translational models remains a firm commitment of this Core and this new project fits this criterion well.
B. Positions and Honors

Positions and Employment

1990    Postdoctoral Fellow, Depart. Neurobiology, Univ. of Southern California, Los Angeles, CA
1991-1993  Postdoctoral Fellow, Divisions of Reproductive Biology and Neuroscience, Oregon National
Primate Research Center (ONPRC), Beaverton, OR
1994-1998  Staff Scientist I, Division of Neuroscience, ONPRC, Beaverton, OR
1999-2008  Staff Scientist III, Division of Neuroscience, ONPRC, Beaverton, OR
1999-current  Head, Primate Aging Resource, ONPRC, Beaverton, OR
2009-current  Senior Staff Scientist, Division of Neuroscience, ONPRC, Beaverton, OR
2009-current  Adjunct Scientist, Advanced Imaging Research Center (OHSU), Portland, OR

Other Experience and Honors

2009-2013  Board of Scientific Directors, American Aging Association
2010-current  Appointment to the Graduate Faculty (OHSU)

C. Selected Peer-reviewed Publications (out of 154 abstracts, papers, book chapters)

Most relevant to the current application

dopamine beta-hydroxylase, choline acetyltransferase, and serotonin in the dorsolateral prefrontal cortex
PMID:22533414
4. Bahjat RF, Williams-Karnesky, RL, Kohama, SG, West, GA, Doyle KP, Spector, MD, Hobbs, TR, Stenzel-
31:1229-42. PMCID: PMC3099644
5. Urbanski HF, Kohama SG, West A, Glynn C, Williams-Karnesky RL, Earl E, Neuringer MN, Renner L,
 correlate with extent of cerebral ischemia-reperfusion injury in the nonhuman primate. Transl Stroke Res

Additional recent publications of importance to the field (in chronological order)

6. Kohama SG, Garyfallou VT, Urbanski HF. (1998) Regional distribution of glutamate receptor mRNA in the
monkey hippocampus and temporal cortex: Influence of estradiol. Mol. Brain Res. 53:328-332. PMID:
9473714.
of estrogen receptor beta (ER-β) mRNA in hypothalamus, midbrain and temporal lobe of spayed macaque:
continued expression with hormone replacement. Mol. Brain Res. 76:191-204. PMID: 10762694
in blood chemistry and hematology variables during aging in captive rhesus macaques (Macaca mulatta).
J. Med. Primatol.30:161-173. PMID: 11515672
Update: Changes in blood chemistry and hematology variables during aging in captive rhesus macaques
(Macaca mulatta). J Med Primatol 33:48-54. PMID: 11515672


**D. Research Support**

**Ongoing Research Support**

**P51 OD011092**

Robertson (PI) 5/01/09 – 4/30/14

NIH/OD  
Non-Human Primate Aging Resource

Major goals of this project are to direct the aging monkey resource at ONPRC including coordination of new research projects, collaborative efforts, longitudinal exams, testing protocols and generating preliminary data.

Role: Staff Scientist/Core PI

**R01 AG029612**

Urbanski (PI) 9/01/07 – 8/31/13

NIH/NIA  
Interacting Impact of Adrenal and Ovarian Aging on the CNS

The goal of this project is to examine how adrenal and ovarian steroids contribute to the maintenance of cognitive function in primates, and to elucidate the underlying neuroendocrine mechanisms.

Role: Co-Investigator

**R01 AG036670**

Urbanski (PI) 4/15/11 – 6/30/16

NIH/NIA  
Cognition in Rhesus Macaques in Relation to Age and Endocrine Status

The goal of this project is to examine how sex steroids contribute to the maintenance of cognitive function in male primates, and to elucidate the underlying neuroendocrine mechanisms.

Role: Co-Investigator

**U01 NS064953**

Stenzel-Poore (PI) 4/20/09 – 3/31/14

NIH/NINDS  
Development of Toll-like Receptor Agonists as Neuroprotectants in Brain Ischemia

The goal of this application is to develop TLR agonists as neuroprotectants in a preclinical model of nonhuman primate stroke. Studies will address optimal dosing and time windows for candidate molecules, as well as gender and age effects on stroke outcome.

Role: Co-Investigator

**R24 ODO11895**

Bethea (PI) 8/16/12 – 6/30/16

Postmenopausal Monkey Resource

This study compares the effect of immediate estrogen (E) replacement after ovariectomy versus delayed E, on aged rhesus monkeys placed on a Western diet. Endpoints include longitudinal assessments of social
behavior, activity, temperature, cognitive function, brain structure, immune function, fat accumulation, glucose metabolism, bone density and postmortem assessments of coronary arteries, breast tissue, fat insulin sensitivity and the brain.
Role: Co-Investigator

**Completed Research Support (last 3 years)**

**W81XWH-09-1-0276**          Sherman (PI)          5/1/09 – 4/30/12
USAMRAA
Therapeutic Remyelination Strategies in a Novel Model of Multiple Sclerosis: Japanese Macaque Encephalomyelitis
The focus of this grant was to develop a novel, non-human primate model of Multiple Sclerosis, called Japanese Macaque Encephalomyelitis.
Role: Co-Investigator

**U54 AI081680**                Nelson (PI)          3/01/09 – 2/28/11
NIH/NIA
Pacific NorthWest Regional Center of Excellence
Project 2: Yellow Fever Vaccination of the Aged and Immunocompromised
The first goal of the PNWRCE was to identify age-related immune system defects to develop new vaccines and supplemental therapies to enhance protection of individuals to NIAID Category A-C pathogens. A second goal of this center was to use systems genetic, chemical, and proteomics approaches to identify therapeutic targets for biodefense and emerging diseases.
Role: Co-Investigator

**CTSA ARRA**                   Rooney (PI)          10/01/09 – 9/30/11
NIH
Creating a Translational Image Processing Core at OHSU’s Advanced Imaging Research Center
Project’s goal was to build a core group of computer specialists to facilitate post-scan processing.
Role: Co-Investigator
**NAME**
Holly E. Hinson

**POSITION TITLE**
Assistant Professor

**EDUCATION/TRAINING**
(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)

<table>
<thead>
<tr>
<th>INSTITUTION AND LOCATION</th>
<th>DEGREE (if applicable)</th>
<th>MM/YY</th>
<th>FIELD OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rice University, Houston, Texas.</td>
<td>B.A.</td>
<td>05/01</td>
<td>Cognitive Science</td>
</tr>
<tr>
<td>University of Texas Health Science Center San Antonio, Texas.</td>
<td>M.D.</td>
<td>05/05</td>
<td>Medicine</td>
</tr>
<tr>
<td>University of Maryland School of Medicine, Baltimore, Maryland.</td>
<td>Internship</td>
<td>06/06</td>
<td>Internal Medicine</td>
</tr>
<tr>
<td>University of Maryland School of Medicine, Baltimore, Maryland.</td>
<td>Residency</td>
<td>06/09</td>
<td>Neurology</td>
</tr>
<tr>
<td>Johns Hopkins University, Baltimore, Maryland.</td>
<td>Fellowship</td>
<td>06/11</td>
<td>Neurosciences Critical Care</td>
</tr>
<tr>
<td>Oregon Health and Science University, Portland, OR.</td>
<td>MCR</td>
<td>06/15 (expected)</td>
<td>Masters of Clinical Research</td>
</tr>
</tbody>
</table>

**Personal statement**
My specialty is in caring for patients with life-threatening neurologic emergencies such as stroke, seizures and traumatic brain injury. With advanced training in intensive care medicine and neurology, my contribution to this proposal will be to provide insight into brain pathology, as well as clinical and neurological outcomes. I am enthusiastic about the development of this primate model of stroke relevant to female studies, as no such model currently exists.

**A. Positions and Honors**

**Positions and Employment**
2011-Present  Assistant Professor, Department of Neurology, Oregon Health Science University School of Medicine

2011-Present  Attending Physician, Neuroscience Critical Care Unit, Oregon Health Science University Hospital

**Honors**

2010  Abstract *Dual Catheters in Severe Intraventricular Hemorrhage* selected for presentation in Critical Care and Emergency Neurology Section Highlights in the Field at the 62nd American Academy of Neurology Annual Meeting, Toronto, Canada.

2010  Awarded a fellowship to attend NINDS sponsored Clinical Trial Methods Course in August 2010 for *Dysautonomia in Traumatic Brain Injury* protocol.

2011  Abstract *Anatomical basis of paroxysmal sympathetic hyperactivity* chosen to be featured as a daily highlight among the best abstracts accepted for presentation at the 24th Annual Congress of the European Society of Intensive Care Medicine.

B. Selected Peer-Reviewed Publications
Most relevant to the current application

Hinson HE, Patterson SL, Macko RF, Goldberg AP. Reduced cardiovascular fitness and ambulatory function in black and white stroke survivors. Ethnicity and Disease. 2007 Autumn;17(4):682-5.


C. Research Support

On-going Research Support

Title: Quantifying Paroxysmal Sympathetic Hyperactivity 7/01/2012-6/30/2014
2012 American Brain Foundation Practice Research Training Fellowship
Sponsor: American Academy of Neurology
Total Direct Cost: $55,000 per year for two years
Principal Investigator: Holly Hinson

Title: Early Hyperthermia after Traumatic Brain Injury 7/01/2013-6/30/2015
Oregon Multidisciplinary Training Program for Emergency Medicine Clinical Research K12
Sponsor: NHLBI grant #1K12HL108974
Total Direct Cost: $100,000 per year for 2 years
Principal Investigator: Holly Hinson