

Overview of Publications, Honors and Grants

The culmination of my research thus far has resulted in **38 peer-reviewed manuscript publications, one book chapter, and 55 abstracts/posters**. Since arrival at Arizona State University (ASU) in 2005, I have had ten manuscript publications, as well as currently an additional three in review. I have also been invited to be a member of the Internal Scientific Advisory Committee for Alzheimer's Disease for Arizona, and have received five awards and honors including **Outstanding Young Investigator of the Year** for 2007 from the Arizona Alzheimer's Consortium and the **2007 Woodside Sustained Community Service Award** for bringing brain science to Arizona classrooms. In fact, ASU faculty, undergraduate and graduate students attended over 100 young students' classrooms via this program. What a joy to hear second graders discussing parts of a neuron and neural transmission. We get welcomed back every year, and I look forward to continuing this important contribution to future generations.

My first priority is to my graduate students. Inherent to that priority, from my perspective, is our laboratory's research. Grant funding provides students with opportunities to contribute to a team effort on a multi-pronged project with ultimately similar goals. It also allows them to perform hypothesis-driven research and follow through with experimental implementation from the derivation of the specific aim to the end product publication. I currently have four graduate students, six undergraduates and two technicians comprising the Bimonte-Nelson laboratory team. Fortunately, I have grant funding to support our research and my students. **I have received nine grants as Principal Investigator, and one as Co-Investigator, since my arrival to ASU**. These include two NIH RO3 grants and a five year NIH RO1 with direct costs of \$1,750,000. This RO1 grant received a 0.5 percentile ranking and began October 2007. I have several collaborative grants, including an Institute for Mental Health Research grant with Dr. Loretta Mayer (Northern Arizona University) to evaluate a novel rodent model of menopause, an NIH Alzheimer's Disease Center Pilot grant with Dr. William Tyler (ASU) to evaluate hippocampal structure and function during aging, as well as a grant from the Evelyn F. McKnight Brain Institute (Tucson, AZ) with the Translational Genomics Institute (TGEN, Phoenix, AZ) to evaluate novel pharmaceuticals to enhance memory. In addition, Dr. Matthew Huentelman (TGEN) and I have just received an NIH RO1 has been funded. There is a four year \$576,257 subcontract to ASU for this four year grant. Our laboratory's contributions will be to cognitively and neurobiologically characterize potentially novel pharmacotherapies to attenuate age-related memory and brain changes.

Our Research Questions

The ultimate and far-reaching research goal of our laboratory is to discover novel therapies to prevent or reverse age- and neurodegenerative- related memory deterioration. A primary focus is the relation between age-related hormone alterations and the trajectory of age-related memory and brain changes. We have multiple, systems-oriented approaches aimed at this overarching theme.

Cognitive and brain changes during aging and reproductive senescence. One approach is to determine changes that occur in the brain and hormone systems in experimentally unmanipulated animals as aging ensues. Once we determine changes that correlate with this degenerative process, we can attempt to prevent or reverse them via pharmacological or non-pharmacological means.

Non-pharmacological means of attenuating age-related memory and brain changes. A second approach we are utilizing is manipulating the animal's prior cognitive experience as aging ensues. This research is funded by an RO3 grant from the National Institute on Aging (I am PI). We have discovered that the "use it or lose it" tenet holds true. This recently completed study revealed that only long-term memory, but not short-term memory, cognitive practice throughout life protected against age-related memory changes. The most exciting finding from this study is that the procedural components of the cognitive task yielded no age-related protection. Thus, cognitive demand is necessary for protection. These data are currently being written into manuscript form, and were chosen for a Society for Neuroscience press release at the 2007 conference.

Ovarian hormone replacement, memory and aging. A third approach we are utilizing is manipulating ovarian hormones and testing effects on age-related memory and brain changes. This has become the main thrust of our research. This research has recently been funded by the National Institute on Aging via an RO1 grant, with funding that began October, 2007 (I am PI). While there is evidence that hormone replacement decreases the detrimental effects of cognitive aging, several controlled clinical trials failed to find positive effects of hormone therapy, and some found detrimental effects. However, while the specific parameters remain to be elucidated,

there is an overwhelming amount of basic science evidence that estrogens exert beneficial effects on the central nervous system, including protection against experimental insult and attenuation of age-related cognitive and brain deterioration.

Hence, despite the null and negative findings of hormone therapy in some clinical trials, the numerous animal and clinical studies showing positive effects of hormone treatment begs the question of what factors help to determine whether hormone replacement therapy acts as a protectant or a risk factor for brain functioning and brain aging.

Given that women are living longer, yet age of spontaneous menopause has remained stable, women are living approximately one-third of their lives in a menopausal hypo-estrogenic state. This underscores the need to determine the “optimal” hormone therapy that will provide benefits while obviating the risks. For the next five years, for this RO1 we will use the aging rodent model to methodically evaluate variations in current hormone therapies, testing whether they attenuate or exacerbate age-related changes in cognition, as well as whether they alter several neurobiological variables related to aging. ***For our RO1 grant, we will perform: (1) A cognitive and neurobiological evaluation varying formulation and dose of estrogen therapy.*** We will compare cognitive and neurobiological effects of estrogenic preparations used in the clinic, as well as novel estrogenic preparations that have promise as a safer and more effective therapy, ***(2) A cognitive and neurobiological evaluation testing whether clinically-used progestins exert negative effects when given alone, or counteract the effects induced by estrogen.*** Women with a uterus must add a progestin to their hormone therapy to offset the estrogen-induced increase in endometrial cancer. We will test therapeutically-relevant progestins that are commonly given to menopausal women, ***(3) Mechanism of estrogen and progesterone’s effects on cognition, when given alone and in combination.*** We will test hypothesized mechanisms underlying our findings that estradiol enhances memory in young and middle-aged, but not aged, ovariectomized (Ovx) rats (Talboom et al., 2008), progesterone impairs memory in aging Ovx rats (Bimonte-Nelson et al., 2004a), and that progesterone counteracts estradiol-induced positive changes in memory and growth factor increases (Bimonte-Nelson et al., 2004b, 2006). We will use pharmacological modulation of systems known to mediate cognitive function, and compare them to hormone effects. We will also evaluate modulation of hormone effects by pharmacological manipulations.

Novel estrogens to enhance memory and alter the trajectory of age-related memory and brain deterioration. This research is in review with NIH as an R01 grant (I am PI). This work is a collaboration with Dr. Laszlo Prokai and Dr. Kati Prokai-Tatrai, medicinal chemists (University of North Texas). ***Numerous studies have indicated that, while the absence of estrogen is not optimal, neither are the currently-used forms of estrogen therapy.*** The research proposed in our studies evaluates a new potential form of hormone therapy, in the context of brain intact (controls) and compromised (stroke) animal models. Estrogens affect multiple non-cognitive systems. Therapies utilizing exogenous estrogens are hampered by undesirable effects in the periphery, including carcinogenic actions on reproductive tissues. A medical need exists for agents that yield positive effects of estrogen on the central nervous system, without the negative effects on reproductive tissue. The proposed research will deliver estrogen to the brain in a novel way, using a prodrug design. ***Prodrugs*** are precursors of therapeutic agents that are inactive until converted to the biologically active agents *in vivo*. In our grant proposal, a prodrug of estradiol will be evaluated, referred to as quinol. Based on the drug’s physicochemical properties, as well as our preliminary data, this treatment is expected to have no impact in the periphery but when in brain, will be converted to estradiol. We recently compared the effects of quinol to estradiol in young Ovx rats. Quinol did not stimulate uterine proliferation, while estradiol did. Moreover, quinol enhanced spatial memory as effectively as estradiol. Our ultimate goal is to find a hormone therapy that will provide the benefits of hormone treatment without the risks. My second year graduate student and I have recently submitted a predoctoral NRSA grant to NIH to further pursue the mechanism of estrogenic effects, and to pursue new estrogenic therapies, in order to ascertain novel therapies.

A novel animal model of menopause. This research has been funded by the Institute for Mental Health Research (I am PI). This work is a collaboration with Dr. Loretta Mayer, a physiologist (Northern Arizona University). Ovarian hormone loss is linked to memory decline in women. There is increasing evidence from the clinical literature that type of ovarian hormone loss may impact subsequent cognitive function. Indeed, women that had surgical menopause via ovary removal exhibited poorer short-term memory scores as compared to women that had undergone natural physiological menopause. The rodent model has been used to evaluate the cognitive and brain effects of ovarian hormone loss. Thus far, the rat model has yielded much insight regarding the cognitive effects of ***surgical*** ovarian hormone loss (Ovx), which models approximately 12% of women. Surgical ovarian hormone loss is an abrupt loss. While the question of the effects of such an abrupt versus

transitional loss of ovarian hormones is important and clinically relevant, until recently basic science researchers did not have the means to evaluate this. Within the last five years Dr. Mayer and colleagues discovered that the compound 4-vinylcyclohexene diepoxide (VCD) results in ovarian follicular depletion in the rodent; in this rat model, after a gradual deterioration of follicles resulting in an ultimately extensive loss of follicular reserves, gonadal hormone and gonadotropin profiles are remarkably comparable to the profile seen in menopausal women. Until the discovery that VCD induces loss of ovarian follicles, there has been no method by which animal researchers could evaluate the cognitive effects of non-surgically-induced ovarian hormone loss in the rat. We now have the capability to address this question in an innovative way, using a model that accurately reflects the physiological presentation of menopause in women.

Final Thoughts and Trajectory Toward the Future

Our laboratory performs interdisciplinary research in animal models using a systems perspective. My long-term research goals are to characterize relations between the brain and cognition, with special relevance to interactions with hormones, and age-related memory deterioration. The ultimate goal is to lead scientific discovery to a translational place whereby our work leads to clinical benefits for aging women and men.

I believe that utilizing rigorous experimental design and diverse learning and memory paradigms that tap into various aspects of cognitive function are the best strategies to decipher the complex correlations between the brain and behavior. It has been my experience thus far that such an interdisciplinary approach is facilitated by strong collaborations within and across departments. Hence, I envision that our laboratory will continue along our current trajectory of collaborations. One of my goals pertains to this point of collaborative work between laboratories, including those which study the human population. Indeed, one of my career goals is to evaluate research questions using a translational approach: from bench to bedside, and bedside to bench. Via our collaboration with Dr. Leslie Baxter at Barrow Neurological Institute, we have begun evaluating brain morphology using MRI scans in menopausal women on and off hormone replacement therapy. We plan to continue asking questions in animal models that are relevant and based on the clinical situation, as well as to perform collaborative clinical research.

Many of the above examples of our animal research utilize the clinical situation to guide our work, hoping to yield insight into mechanisms of hormones and therapies used in the clinic to discover new treatments or enhance current ones (thus looking, initially, from human to animal). However, our approach is, in fact, multi-pronged. Indeed, we also are obtaining information from molecular discoveries to guide us in our quest for memory- and brain- enhancing therapies (thus looking from molecular to animal to, eventually, human). In my collaboration with TGEN, we use gene expression in cognitive brain areas to mark novel systems that may be compromised with aging and neurodegenerative disease. The goal here is to enhance cognition and brain function by discovering novel pharmaceutical therapies. It is my hope that my laboratory's research will continue along the current trajectory of research funding and discoveries that yield insight into the neurobiological and hormonal basis of age-related memory change, eventually resulting in therapies in the clinic. As I have the pleasure of watching my undergraduate and graduate students grow and discover new scientific findings along with me, I am certain that watching them develop into inspired scientists tackling difficult scientific questions will be my ultimate reward.