



Wake Forest University
PRIMATE CENTER
NEWSLETTER

Spring 2011

The mission of the Wake Forest University Primate Center (WFUPC) is to use nonhuman primates as human surrogates to conduct research on normal biological processes, their disruption by disease, and therapeutic interventions. To that end, the Center's goal is to extend understanding of environmental and genetic contributions to health and disease as seen in both sexes and across the lifespan.

What can Nonhuman Primates Tell Us about Aging and Disability?

Kevin P High, MD, MS, FACP, FIDSA, Professor of Medicine and Translational Sciences
Chief, Section on Infectious Diseases

Our nation is headed for an “age wave” that will drive social, political and economic agendas for the next two decades. Illness and physical disability are common in seniors, particularly those beyond 80 years. Older adults comprise more than half of all long-term care residents (Fig. 1). Moreover, physical disability reaches nearly 50% for community-dwelling seniors age 75 years and over (Fig. 2). Epidemiologic investigations – such as those conducted through the NIA-funded Claude D. Pepper Older Americans Independence Centers – have begun to illuminate the mechanisms leading to disability in seniors.

Long Term Care Recipients By Age

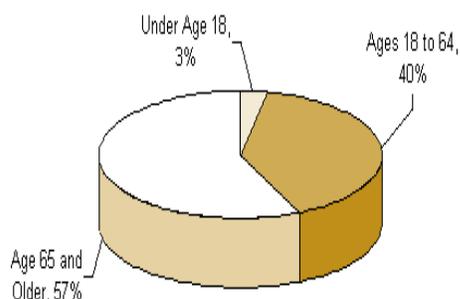


Figure 1

Percent of Noninstitutionalized U.S. Population With Limitations of Activity Caused by Chronic Conditions

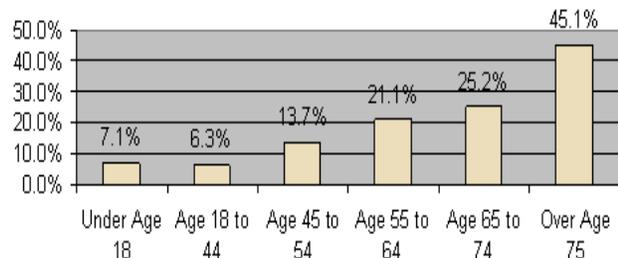


Figure 2

However, mechanistic studies in human subjects are limited to manipulations known to be safe (e.g. dietary and exercise interventions). Furthermore, while invertebrate and rodent models of aging have been valuable for investigations precluded in humans by ethical concerns or logistical constraints, these platforms do not reflect the complex biologic, social, genetic, and environmental processes required to apply systems biology approaches to the investigation of disability prevention and age-related illness. Thus, **there is a critical need for animal models that closely mimic human aging and functional disability to facilitate “healthspan” research** – i.e., research focused on the factors that preserve health and function into advanced old age.

Further, animals that can model disability in aging women are likely to have the greatest societal impact, as the majority of 80+ adults are women, and in that age group women are more likely than men to become disabled and require long-term care. This is true in part because women live longer than men, but also because many of the major causes of disability (e.g. arthritis, dementia) are more common in women than men at the extreme of human lifespan (85+ years).

(Continued on page 2)



**FROM THE
DIRECTOR**

**JAY R KAPLAN,
PHD**

I thought it would be timely to devote this commentary to the proposed plan to disaggregate the National Center for Research Resources (NCRR). Most investigators are aware that the suggested reorganization of the NCRR has left unresolved the future of the Division of Comparative Medicine (DCM). The DCM currently comprises the resource grants that facilitate the development and application of a broad spectrum of animal models (including the nonhuman primate programs), informatics resources that increase the utility of the large genetic and genomic databases required to make systems biology a reality, and research grants that improve animal resources and thereby enhance the ability of the NIH categorical institutes to conduct disease-specific investigations. Additionally, the DCM supports the training grants necessary to educate and provide research experience to each new generation of comparative medicine scientists, who are central to the conduct of translational and basic research using animal models. Wake Forest University houses one of the Nation's oldest and most prominent academic primate centers. We also represent one of the NIH's senior programs in comparative medicine. Because comparative medicine as a discipline is not species specific, we believe strongly that any fragmentation of the DCM's research, resource, and training programs would be detrimental to the advancement of both translational and discovery research. History demonstrates that DCM programs and activities have enabled the NIH's categorical institutes and centers to take advantage of the full continuum of animal models and thereby enhance human health and well-being. Accordingly, we have taken the position that the DCM should remain intact as an administrative structure, wherever this entity may be located.



(Continued from page 1)

Their numerous resemblances to human beings make Old World monkeys an attractive alternative to other models for studying the intricacies of aging and disability, particularly with regard to women's health. However, there are relatively few monkey colonies of sufficient size and adequate characterization to provide the basis for such investigations. One exception is the African green monkey (AGM) research Colony at the Wake Forest University (WFU) Primate Center, a fully pedigreed and genotyped population of approximately 425 *Chlorocebus aethiops sabaesus* ranging in age from 0 -26 years and heavily weighted with females (> 300). This population is derived from 57 founder animals captured on St. Kitts and maintained as a closed colony since the early 1980s. Exact pedigrees and ages are well documented in the colony, which has been used primarily for neurobehavioral and cardiometabolic research. Since all AGMs on St. Kitts (and by extension in the WFU colony) were derived from a relatively limited number of animals transported to the Caribbean from Africa about 400 years ago, the resulting WFU colony likely represents a population that is relatively constrained genetically and offers two kinds of advantages: 1) in a sense, the population is reminiscent of the highly related animals (i.e., strains) often used for rodent studies; and 2) the progenitor population can still be accessed on St. Kitts should genetic variants of interest be identified in the WFU population. These characteristics establish the possibility of genetic matching, a powerful tool that provides opportunities for both observation and intervention cohorts to examine the physiologic, social and genomic factors that lead to senescence, organ-system dysfunction and frailty/physical disability.

Recognizing the unique nature of the WFU AGM colony, the WFU Pepper Center has supported a number of pilot investigations that demonstrate our capacity to develop this species as a longitudinal model of aging and disability, and one capable of facilitating mechanistic investigations across multiple organ systems. Our approach to model human aging with this AGM population focuses on the theme that inflammation pathways promote age-related organ dysfunction, physical decline and frailty. The overall goal is to detail relevant aspects of the AGM as it ages, and use this information to derive an "immune-risk phenotype" and a physical function index that parallel human studies. Preliminary data have been gathered regarding physical function, body composition, immune responses to vaccines, genetic diversity of key genomic regions (e.g. MHC), and epigenetic changes in response to dietary interventions. Additional information on muscle function, cardiovascular function, and tissue-specific changes in body fat depots, kidney, heart, and brain tissues are currently being collected. We believe this new animal model will be a powerful ally in the effort to discover interventions that can reduce disability and preserve health for our aging senior population.



Spotlight on Extramural Investigator: Alex Polotsky

Obesity and female reproduction

Up to 2% of U.S. couples experience recurrent early pregnancy loss. While the prevalence of obesity in patients with recurrent pregnancy loss is not well determined, obese women have higher rates of spontaneous miscarriage and recurrent miscarriage than their lean counterparts. Mounting evidence from clinical trials suggests that corpus luteum insufficiency may underlie some cases of spontaneous abortion in women with recurrent pregnancy loss. However, early pregnancy loss (EPL) represents a heterogeneous clinical entity. We have just undertaken a project designed to model EPL using adult female vervet monkeys (*Chlorocebus aethiops sabaeus*) fed an obesity-promoting diet (i.e., relatively high in fat and simple carbohydrates). By assessing hypothalamic-pituitary-ovarian hormone function before and after obesity acquisition, we hope to define the mechanisms by which adiposity induces reproductive derangements. We will also assess the effects of obesity on luteal function by examining the differential gene expression profile of corpus luteum tissue. The results should allow a more complete characterization of markers of reproductive incompetence in obese women.

Following validation of the microar-



Alex Polotsky, MD, MS
Assistant Professor
University of Colorado Denver, Department of Obstetrics
and Gynecology

ray findings with qRT-PCR, we plan to further refine the phenotype that comprises obesity-caused changes in the primate corpus luteum. Thus we will utilize the corpus luteum tissue sections to perform immunohistochemistry to confirm gene expression data on the protein level and examine tissue compartmentalization. We anticipate identification of novel molecular markers that may explain corpus luteum insufficiency and impaired progesterone secretion that is well characterized in human obesity.

Our next step will be devoted to examining the translational relevance of our findings in humans. In this re-

gard, we anticipate our results will aid in identifying specific subgroups of women who are truly deficient in progesterone secretion. Ultimately, we intend to translate the NHP findings to studies of clearly defined subsets of patients. Specifically, we will assess obese women undergoing in vitro fertilization as well as obese women undergoing preimplantation genetic diagnosis and in vitro fertilization for unexplained recurrent pregnancy loss. The foregoing approach involves harvesting luteinized granulosa cells at the time of egg retrieval, a methodology that has been successfully used at our institution.

We believe that vervet monkeys have the potential to enable development of novel biomarkers and possible therapeutic targets likely linked with impaired early pregnancy maintenance in humans. This development would improve our understanding of EPL on a mechanistic level. Finally, pending the outcome of the gene expression microarrays, we will consider extending our survey to include alterations in microRNA processing that are known to regulate gene expression such as those described as a cause of corpus luteum insufficiency and infertility in mice.

AALAS Awards

Congratulations to Animal Resources Program (ARP) employees, **Vickie Hardy**, CMAR, RLATg, Operations Manager, Friedberg Campus and **Joy Brinkerhoff**, LATg, LAR Supervisor, Bowman Gray Campus on receiving awards at the annual Research Triangle Branch (RTB) AALAS (American Association for Laboratory Animal Science) Awards Banquet in Research Triangle Park, N.C. **Vickie** was presented with the *Manager of the Year Award* and received a plaque and a gift card from Allentown Caging Equipment Co. **Joy** was chosen for the Purina Mills Pro-Lab Award as *Laboratory Animal Technician of the Year* and she also received a plaque and a gift card. Vickie and Joy were selected for exemplifying outstanding dedication and service to the field of Laboratory Animal Care.

Primate Center Symposium

June 9 — The Aging Primate Brain: A Multi-System Approach

The aging process affects all systems, including the central nervous system. This symposium explores the general concept that the tempo and pattern of changes in the aging primate central nervous system both reflect and contribute to changes in other bodily systems. Individual presentations are designed to describe the most common changes that occur in the brains of aging monkeys, and to begin exploring those that may be occurring concomitantly in other systems as animals transit the lifespan. Discussion will focus on: 1) the identification of changes in somatic systems that may influence brain aging, and changes in the brain that may influence the aging of somatic systems; and 2) the identification of key questions about multi-system interactions which affect brain aging that might be most profitably addressed in nonhuman primates.

Please contact Melody Hooker at mhooker@wakehealth.edu for more information.

PRIMATE CENTER RESOURCES AND CONTACT INFORMATION

Tissue and Data Repository

The WFUPC has an extensive repository of tissues and biomarker, anthropometric, and behavioral data from over 11,000 animals representing both Old and New World species. For information on these samples or to request access to this repository, please contact Mark Cline, DVM, PhD (jmcline@wakehealth.edu). To request access to the data, please contact Matthew Jorgensen, PhD (mjorgens@wakehealth.edu).

Breeding Colony Resources

Two NCCR-supported breeding colonies (*M. fascicularis* and *C. aethiops*) are specifically designated as national research resources. Animals in the colonies can be used for genetics-based studies of behavior or diseases, and would be especially valuable for researchers at institutions that do not have NHP housing available. Scientists interested in using these colonies can access blood or tissue samples collected from the colony, or can lease or purchase animals directly for either on-site or off-site studies.

Scientists wishing to access colony resources or purchase monkeys should contact Matthew Jorgensen, PhD, Assistant Director for Intramural Collaborations (mjorgens@wakehealth.edu). Wake Forest University is a USDA-licensed primate dealer.

Small intramural grants may be available to support pilot studies. Contact Jay Kaplan, PhD, Director of the WFUPC (jkaplan@wakehealth.edu) for more information.

There is also a bonnet macaque (*M. radiata*) breeding colony, one of only two in the United States. Animals are from a multi-generational pedigree and range from infant to aged; they are comprehensively characterized for behavioral and neurobiological development across the lifespan. For information concerning collaborative research or access to this colony, please contact Allyson Bennett, PhD at abennett@wakehealth.edu.

Training

Post-DVM training is available through an NCCR-supported T32 Post-Doctoral Research Fellowship program, currently in its 52nd consecutive year of funding. Institutionally supported residencies in Laboratory Animal Medicine and Veterinary Anatomic Pathology are also available, as is a summer student research program for veterinary students (supported by an NCCR-funded T35 training grant) and externships for senior veterinary students. For more information, contact Mark Cline, DVM, PhD, Director of Training (jmcline@wakehealth.edu).

Community Outreach

The Wake Forest University Primate Center's outreach and education program serves the community by providing children in grades K-12 and their teachers with opportunities to visit the WFUPC and learn about biomedical research. These tours are designed to give visitors educational information about nonhuman primates and the unique role that they play in translational research, to highlight the wide range of human health disorders that are addressed by the Translational Science Institute and the WFUPC, and to educate children about careers in science. We have initiated the "Innovative Evaluation and Promotion of Evidence-Based Enrichment" program as a new outreach activity aimed at enhancing our environmental enrichment program for non-human primates while providing undergraduate students with research opportunities. Undergraduate students from Wake Forest University and Salem College are currently participating. For more information, contact Allyson Bennett, PhD, Assistant Director for Community Outreach and Education (abennett@wakehealth.edu).