



CALIFORNIA NATIONAL PRIMATE RESEARCH CENTER

The mission of the California National Primate Research Center (CNPRC) is to improve human health and quality of life through the support of exceptional nonhuman primate research programs.

The CNPRC is one of seven centers supported by the National Institutes of Health (NIH), Office of the Director. The National Primate Research Centers are a unique resource for investigators studying human health and disease. They offer the opportunity to assess the causes of disease and new treatment methods in nonhuman primate models that closely recapitulate humans, providing essential information before proceeding to human clinical trials that lead to new therapies and surgical procedures that benefit human health and quality of life. <http://www.cnprc.ucdavis.edu>

The CNPRC has a diverse program encompassing many aspects of biology and medicine from basic to translational research, focused into four primary areas:

Brain, Mind, and Behavior. Neuroanatomical and biobehavioral organization, neuroimmune interactions and the etiology of autism, social bonds and social development, the human-animal interface, and social networks. Specialize in research on sociality, temperament, and development with a lifespan approach that utilizes measures from early stages to aged animals, including new primate models of human psychiatric diseases.

Infectious Diseases. Preclinical / translational studies on a wide range of viral and bacterial pathogens (e.g., SIV, cytomegalovirus, H. pylori), vaccine and drug interventions, and mechanisms of host-microbe interactions. Lifespan-related research through studies that focus on the impact of age on infection, pathogenesis, and vaccine efficacy.

Reproductive Sciences and Regenerative Medicine. Gamete biology and reproductive toxicology, fetal models of congenital and acquired diseases, unique strengths in gene- and cell-based therapy / regenerative medicine and tissue engineering tailored to age across the lifespan. Long-standing commitment to development and application of novel in vivo imaging technologies and tools (e.g., ultrasound, optical imaging, PET/CT), and studies that focus on healthy aging, the menopausal transition, and the impact of environmental agents on reproduction and development.

Respiratory Diseases. Airway development and remodeling, age-related impact of environmental exposure, and lung immunity – asthma, environmental tobacco smoke, influenza, and chronic obstructive pulmonary disease. Unique areas of expertise in pulmonary research from toxicology and neurophysiology to immunology and airway remodeling. Major emphasis is pediatric models of lung disease with an overall goal of understanding how early life environments impact health outcomes with maturity.

Established in 1962, the CNPRC is located at the University of California, Davis on 300 acres. The center's staff of around 300 individuals is comprised of scientists; veterinarians; animal care technicians; specialists in pathology, animal husbandry, behavior and enrichment; undergraduate, graduate, and postdoctoral students and other trainees; and laboratory and administrative personnel.

Members of the scientific staff – representing a variety of disciplines including cell and developmental biology, genetics, psychology, physiology, reproductive biology, development, virology, and immunology – hold joint appointments in academic departments in Schools (e.g., Medicine and Veterinary Medicine) and Colleges (e.g., Engineering, Letters and Science) on the UC Davis campus. Affiliate Scientists collaboratively work with Core Scientists and conduct research projects in their area of interest and benefit from the extensive expertise of the scientific staff.

OTHER CAPABILITIES. The CNPRC has service Cores and other associated service opportunities for investigators, including: Behavior Research Services Core, Endocrine Core, Immunology and Pathogen Detection Resources Core, Inhalation Exposure Core, and Multimodal Imaging Core; Anatomic and Clinical Pathology Services; Primate Medicine Services; Genetics Services; Clinical Proteomics; Host-Microbe Systems Biology; the NHLBI Center for Fetal Monkey Gene Transfer for Heart, Lung, and Blood Diseases; and specialized facilities in the Respiratory Disease Center and the Translational Human Stem Cell Shared Research Facility. These services and facilities provide expertise and resources to support research for scientists nationally and internationally. <http://www.cnprc.ucdavis.edu/our-services/>

WHY MONKEYS? Virtually every major medical advance of the last century has relied on animal research. The knowledge gained through such research has led to the ability to treat, prevent, or eradicate human diseases. Research on animals benefits wild and domestic animals, people and the environment, and has resulted in many lifesaving treatments and therapies. When studying human diseases, nonhuman primates provide one of the best animal models because they are similar to humans. Humans and monkeys bear a close genetic relationship, reflected in many anatomical, behavioral, developmental, physiological, immunological, reproductive, and developmental similarities. Because of these close similarities, nonhuman primates have played a critical role in biomedical and behavioral research. <http://www.cnprc.ucdavis.edu/animals/why.aspx>

- For example, monkeys are susceptible to an immunodeficiency virus similar to HIV, making them ideal for the study of AIDS and potential vaccines and treatments.



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- Similarities in the central motor pathways between monkeys and humans have led to the development of safe and effective interventions to slow the progress of Parkinson's disease.
- Monkeys in breeding colonies can live well past their typical lifespan in the wild, providing opportunities for research on aging-related diseases, such as Alzheimer's disease and changes associated with the menopausal transition and reproductive senescence. Studies at the CNPRC have led to successful clinical trials and beneficial treatment of people with Alzheimer's Disease.
- Monkeys are the only animal model with a menstrual cycle and hormonal patterns comparable to humans. Thus, reproductive research provides crucial insights into fertility, pregnancy, and the menopausal transition.

ANIMAL CARE. The CNPRC houses approximately 5,000 monkeys for research and breeding, and has one of the best animal care programs in the nation as evident in the continued accreditation of the UC Davis Animal Care Program by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC) International. The majority of the monkeys are rhesus macaques (*Macaca mulatta*), with a small population of South American titi monkeys (*Callicebus cupreus*). There are no chimpanzees, gorillas, or other apes at the CNPRC. Many of the monkeys live at the CNPRC for decades in social groups in half-acre outdoor corals. Approximately 600 infants are born each year, primarily in the spring. The center also houses an aged colony of monkeys, ranging in age up to 38 years. The CNPRC is focused on expanding its colony of "specific pathogen free" or SPF monkeys. SPF monkeys are bred to be free of several viruses that, while harmless to monkeys, can have severe and sometimes fatal consequences if contracted by humans. <http://www.cnprc.ucdavis.edu/animals/care.aspx>

In addition, the CNPRC has an excellent Environmental Enrichment Program for the benefit of all animals, indoors and outdoors. The goal is to provide daily enrichment and to facilitate psychological well-being through provision of multiple forms of environmental enrichment.

OVERSIGHT AND REGULATIONS. As required by federal regulations, anyone conducting research or using animals for teaching at UC Davis must first document there are no viable alternatives to the use of animals for the objective of their research or teaching, or if there are potential alternatives, why these alternatives are not adequate. In addition, the UC Center for Animal Alternatives, established by the California Legislature in 1991 and located at UC Davis, has aided in the refinement in the number of animals used in teaching and research. This program encourages the development and use of alternative models such as computer programs where feasible.

The campus Institutional Animal Care and Use Committee (IACUC) must approve each animal research and teaching project before it can begin. This review process is mandated by federal law and to maintain compliance with the Public Health Service (NIH) guidelines on humane care and use of laboratory animals. The IACUC must verify that the living conditions of the animals are appropriate for the species, that the use of pain-relieving drugs is adequate, and that the numbers of animals are the minimum necessary to conduct the project.

Animal welfare inspectors from the U.S. Department of Agriculture regularly perform routine unannounced inspections of the campus, also as required by federal law. Campus facilities are also inspected and accredited by AAALAC International as noted above as a component of the overall accreditation process.

Studies at the CNPRC must pass three levels of review prior to initiation. The CNPRC's Research Advisory Committee reviews all proposed projects to ensure feasibility for conduct at the Center, that the techniques and methodologies proposed are appropriate, and that the study justifies the use of nonhuman primates (most of which are bred on the premises). If approved by the Research Advisory Committee, the project must then be reviewed and approved by the campus IACUC. Additionally, the proposed research is reviewed at the level of the funding agency such as the NIH. <http://www.cnprc.ucdavis.edu/research/condres.asp>

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Other potential information sources:

California National Primate Research Center
<http://www.cnprc.ucdavis.edu>

Foundation for Biomedical Research:
<http://www.fbresearch.org/>

California Biomedical Research Association:
<http://www.ca-biomed.org/>



RECENT TRANSLATIONAL RESEARCH ACCOMPLISHMENTS

For more details, see: <http://cnprc.ucdavis.edu/news-archive/>

The Importance of the Monkey Model. A recent collaboration of CNPRC Core Scientists John Capitanio, Karen Bales and Lisa Miller, along with other national experts, addressed the importance of nonhuman primate models for advancing knowledge in biomedical and biological research. Presenting a forthright discussion of the ethical considerations of using nonhuman primates in research, they demonstrate the vital role these animals have played in many of the medical and scientific advances of the past 100 years.

BRAIN, MIND, AND BEHAVIOR RESEARCH UNIT

Loneliness and Health. Loneliness can be a significant cause of poor health, and is of special concern in the elderly. However, not all people, nor animals, have the same level of desire to be social. It is the choice of sociality, and the behavioral consequences when there is a disconnect between the desire to be social and the reality of social interaction, that was the focus of a research study by John Capitanio, PhD, Core Scientist. Results from these human and monkey studies suggest that nonhuman primates may provide a valuable animal model to better understand how chronic loneliness contributes to poor health as people age.

Maternal Antibodies Linked to Autism. In a major advance in understanding risk factors, and possible means of prevention of autism, Melissa Bauman, PhD, Affiliate Scientist, and David Amaral, PhD, Core Scientist, performed studies at the CNPRC with rhesus monkeys to further define the role that maternal antibodies may play in the risk of having a child having autism.

Improving Models to Understand the Etiology of Autism. Using an exciting, first of its kind method and making great strides in understanding the biology of autism, Sara Freeman, PhD, postdoctoral fellow at the CNPRC, was the first to develop a novel protocol to noninvasively locate and map oxytocin brain receptors in rhesus and titi monkeys. Similar to humans, macaques and titi monkeys naturally show a spectrum of sociality and have great potential for elucidating the neural mechanisms by which oxytocin modulates social cognition, which has implications for oxytocin-based pharmacotherapies for psychiatric disorders such as autism and schizophrenia.

Unknown Effects of Long-term Oxytocin Use in Children. Core Scientist Karen Bales, PhD, is particularly interested in the role of neuropeptides such as oxytocin and vasopressin in social bonding and male parental care, as well as the effects of early experiences on the development of these behaviors. From her research Dr. Bales has shown that even a single dose of oxytocin can have long-lasting effects: “The clearest message was that any exposure to oxytocin can cause long-term behavioral and neuroendocrine effects. There’s been this quick leap from looking at a single dose of oxytocin in healthy adults to administration to children with autism whose brains are still developing,” she says. Her research findings raise the troubling possibility that repeated use of oxytocin nasal spray may cause long-term changes in the brain that negate or even reverse the hormone’s benefits, perhaps by tricking the brain into producing less oxytocin.

INFECTIOUS DISEASES RESEARCH UNIT

Breast- and Bottle-fed Infant Monkeys Develop Different Immune System. In a study published in *Science Translational Medicine* on September 3, 2014, researchers from the CNPRC at UC Davis, including Core Scientist Dennis Hartigan-O’Connor, MD, PhD, and from UC San Francisco have shown that breast- and bottle-fed infant rhesus macaques develop different immune systems. Although the researchers expected that different diets would promote different intestinal bacteria, they found a broad extent to which these bacteria shaped immunologic development.

Vaccine Fends Off Virus that Strikes Weak Immune Systems. Core Scientist Peter Barry, PhD, led studies on an experimental vaccine modeling human cytomegalovirus (HCMV) infection – which can endanger developing fetuses, transplant recipients, patients co-infected with HIV and others who have a weakened immune system. The vaccine proved safe and effective in research using the rhesus macaque model and developed the first-of-its-kind approach to preventing HCMV infection inducing broader immunological protection.

Combination of Adjuvant with Influenza Vaccine Results in Dramatic Increase in Protection of Aged Rhesus Macaques. Studies by Core Scientist Christopher Miller, DVM, PhD, showed that a combination of adjuvant with influenza vaccine resulted in enhanced immunity and provided superior protection in elderly rhesus macaques, and protected these immunized primates against challenge with live influenza virus. These studies highlight the importance of addressing age and efficacy of vaccines to protect against human disease, particularly in the elderly.

Tenofovir Component of Successful Prophylaxis for HIV Prevention. Tenofovir (Viread), an antiretroviral HIV drug first shown at the CNPRC by Affiliate Scientist Koen Van Rompay, DVM, PhD, to be safe and effective in treating monkeys that were infected with SIV, has once again been used as the key ingredient in successful HIV preventive studies. The two new studies, supported by the Bill and Melinda Gates Foundation and the U.S. Centers for Disease Control and Prevention, found that daily pills formulated with tenofovir lowered the risk of HIV infection by up to 73% when given to uninfected heterosexual men and women in Africa who have an HIV-infected partner. This brings new hope for someday offering a medical shield against HIV infection.



REPRODUCTIVE SCIENCES AND REGENERATIVE MEDICINE RESEARCH UNIT

Menopausal Transition and Health Outcomes. Studies by Core Scientist Bill Lasley, PhD, have been instrumental in understanding the unique differences that may occur between women during the menopausal transition, and how this may impact health. Using a comparative human and nonhuman primate approach, a new and provocative aspect to the endocrine foundations of the menopausal transition have been shown which may provide important clues to understanding the fundamentals of mid-aged women's healthy aging, particularly as it relates to the different responses to hormone replacement therapies. For example, studies using the nonhuman primate model have provided critical insights into the relationship of changes in adrenal gland function to symptoms and health outcomes of mid-aged women.

Plastics Chemical Shows the Potential for Two-Generation Effect and Could Lead to Breast Cancer. BPA (bisphenol A) is used in the manufacturing of various plastics and food packaging, consumer products, some paper receipts, and medical devices. Exposure of pregnant monkeys to BPA was shown to disrupt fetal ovarian development, potentially resulting in birth defects and reproductive problems that would not emerge for a generation, according to research by Core Scientist Catherine VandeVoort, PhD, and Patricia Hunt, PhD, and colleagues at Washington State University. The study of BPA in a primate model is critical because the rhesus monkey has estrogen levels as well as reproductive and developmental processes that are similar to humans, and very different than rodents. The results of this study are highly relevant to human health as the amount of BPA given produced blood levels that are slightly lower than the mean level measured in humans. Co-investigator Dr. Ana Soto, Tufts University, noted: "Our results suggest that it is very likely that fetal exposure to BPA would also increase the propensity to develop mammary cancer in monkeys". In related studies with Affiliate Scientist Laura Van Winkle, PhD, an increase in mucin genes and mucous cell maturation in fetal lungs was observed.

Tracking Tissue Engraftment and Transplant Efficiency. Studies by Core Scientist Alice Tarantal, PhD, and national collaborators have defined the timeline of kidney development in order to apply tissue engineering approaches to regenerate kidneys damaged by disease. Successful treatment of human diseases with stem and progenitor cells requires safe, reliable, and reproducible measures of engraftment to monitor cell viability and function. Studies conducted by Core Scientists Tarantal and Simon Cherry, PhD, are revolutionizing the ability to monitor cell transplant efficiency, using noninvasive imaging methods that have demonstrated engraftment and long-term safety.

Gene Therapy for Treatment of Congenital Disease. Collaborative studies involving Core Scientist Alice Tarantal, PhD, used a new gene therapy strategy in the rhesus monkey to enhance synthesis of acid alpha-glucosidase, an enzyme involved in degradation of glycogen. Humans who are deficient in acid alpha-glucosidase by virtue of an autosomal recessive genetic mutation develop a glycogen storage disorder called Pompe disease. Results from studies in monkeys enabled a pre-investigational new drug (IND) submission to the Food and Drug Administration – this approach is now in clinical trials for use in 3- to 14-year-old Pompe patients with ventilator dependence.

RESPIRATORY DISEASES RESEARCH UNIT

Long-term Health Impacts of Wildfire Smoke Exposures. California wildfires in 2008 led to a natural experiment with monkeys living outdoors at the CNPRC that address gaps in our understanding of the effects of air pollutant exposure during early life. Core Scientist Lisa Miller, PhD, led the project, showing for the first time that acute exposure to high levels of fine particle pollution affects both development of the immune system and lung function in a long term-fashion.

Postdoctoral Fellow Works to Identify Pediatric Lung Defenses. Candice Clay, PhD, a postdoctoral fellow in the CNPRC Respiratory Diseases Research Unit, was awarded a two-year Hartwell Postdoctoral Fellowship, to help to identify mechanisms that limit pediatric defense against viruses and bacteria in the lung. Approaches to augment innate immune function of infant lungs may ultimately translate into improved therapeutics and vaccines for the highly susceptible pediatric population.

An Inhibited Temperament May Predict Asthma. In a collaboration between CNPRC Brain, Mind and Behavior Research Unit Core Scientist John Capitanio and Respiratory Diseases Research Unit Core Scientists Edward Schelegle, PhD, Lisa Miller, PhD, and Dallas Hyde, DVM, PhD, a naturally occurring behavioral phenotype characterized as inhibited in temperament was found to be significantly associated with the development of adult asthma. Strikingly, animals that were identified as having an inhibited temperament at infancy were shown to exhibit heightened responsiveness to non-specific triggers of airways reactivity, which is diagnostic of asthma in humans.

Neurotransmitter Linked to Childhood Asthma. Using a nonhuman primate model of childhood asthma developed by Core Scientist Edward Schelegle, PhD, and colleagues have shown that the establishment of enhanced smooth muscle contractility during early life appears to be mediated by the neurotransmitter serotonin. The induction of this phenotype in nonhuman primates was mediated by environmental exposures to air pollution and allergens, substantiating the need to minimize exposure of young individuals during critical periods of lung maturation.