Understanding Early HIV Infection
And identifying potential therapeutic targets

The mucosal lining of the human gastrointestinal tract is on the frontline of immune defenses, crucial in preventing infection and controlling the spread of intestinal pathogens. It must respond rapidly to eradicate pathogens, while simultaneously maintaining tolerance to commensal bacteria. This balance is critical to the maintenance of intestinal homeostasis.

When an individual is first infected with HIV, the virus causes a breach in the mucosal defense and the gut goes through a series of responses that lead to deficiencies in the immune system and defects in the epithelial barrier, which result in chronic inflammation, disease progression, and an increased susceptibility to pathogens. In HIV-infected individuals, systemic immune activation is also increased through a translocation of intestinal microbial products into the systemic circulation.

The biology behind this breakdown in the integrity of the gut barrier has been well studied, but what happens before this cascade of events was not understood until the following research study was conducted at the CNPRC at UC Davis.

Sayta Dandekar, Ph.D., Core Scientist in the CNPRC Infectious Disease Unit, Professor and Chair Medical Microbiology and Immunology, UC Davis School of Medicine, is using the rhesus monkey model of HIV, Simian Immunodeficiency Virus (SIV), to investigate early state dysfunction in the gut mucosal response and to determine the mechanisms contributing to the inability of the host to control these infections. This knowledge will be crucial in identifying therapeutic targets for mucosal protection against the virus and co-infections.

To conduct her research, Dr. Dandekar teamed with veterinarians from CNPRCprime medicine services and investigators from across UC Davis – Departments of Medical Microbiology and Immunology, Molecular and Cellular Biology, Biochemistry and Molecular and Food Science.

The research results were published in August 2014 PLOS Pathogens (“Early mucosal sensing of SIV infection by paneth cells induces IL-1β production and initiates gut epithelial disruption”).

A focus of the investigation was Paneth cells, an integral part of gastrointestinal tract immunity. Paneth cells are one of the principal cell types in the epithelial lining of the small intestine and play a crucial role in epithelial cell renewal, immunity and host-defense, and produce antimicrobial substances that have been shown to have a significant effect on bacteria. While the mechanism by which Paneth cells sense and respond to pathogenic bacteria is well characterized, our understanding of their response to HIV infection is limited.

Dr. Dandekar’s research has shown for the first time that Paneth cells play a key role as the earliest detectors in sensing and responding to the virus and as first line responders in setting the stage for the induction of gut inflammation. In animals infected with SIV, the presence of virus within gut epithelium is co-localized with Paneth cells. Moreover, Paneth cells appear to respond to the virus by producing interleukin-1β, an important mediator of the inflammatory response.

This study highlights the need for future investigations to determine the mechanisms of Paneth cell sensing and response to viral infections, and to clarify the importance of the gut epithelium in HIV infection. Understanding is sought for the gut epithelium as not just a target of disease but also as initiator of immune responses to viral infection, which can be strongly influenced by commensal bacteria.

Another focus of the study investigated, for the first time, the immune response by the gut mucosa to commensal bacteria (such as Lactobacillus plantarum) in the context of early HIV infection. The researchers found that the host maintains its ability to distinguish pathogenic (Salmonella typhimurium) and commensal bacteria and mount the proper immune response.

The research findings also suggest a supportive role of commensal bacterium L. plantarum in overcoming SIV-induced gut inflammation and epithelial disruption, raising the possibility of using L. plantarum to intervene the early mucosal-viral interactions that may influence gut inflammation. In addition to its anti-inflammatory effects, they observed enhanced recruitment of T helper 17 cells (which can give rise to protective cells) in response to L. plantarum, suggesting a supportive role of L. plantarum in overcoming SIV-induced gut inflammation and epithelial tight junction disruption. This recruitment of T helper 17 cells may have a role in epithelial repair.

What is potentially exciting about this research is the demonstration that the early stages of gut inflammation and damage caused by infection can be intervened by the targeted probiotic bacteria,” states Dr. Dandekar. However, the findings also discovered unintended consequences that an L. plantarum probiotic therapeutic agent may include the establishment of silent viral reservoirs. The results raise an important consideration in the development of probiotic therapies for HIV infection, and highlight the need for better characterization of probiotic bacterial functions and effects. By understanding the mechanisms that underlie the host / microbiota relationship in health and HIV disease, it will be possible to capitalize on their evolved synergy while identifying gaps in mucosal defenses that can be fortified through therapy.

Surprisingly, these differences persisted for months after the macaques had been weaned and placed on identical diets, indicating that variations in early diet may have long-lasting effects.

“We saw two different immune systems develop: one in animals fed milk and another in those fed formula,” said Dennis Hartigan-O’Connor, M.D., Ph.D., and Core Scientist in the CNPRC’s Infectious Diseases Unit and Reproductive Sciences and Regenerative Medicine Unit, and assistant professor in the Department of Medical Microbiology and Immunology at UC Davis. “But what’s most startling is the durability of these differences. Infant microbes could leave a long-lasting imprint on immune function.”

Dr. Dandekar – Departments of Medical Microbiology and Immunology, UC Davis School of Medicine, is using the rhesus monkey model of HIV, Simian Immunodeficiency Virus (SIV), to investigate early state dysfunction in the gut mucosal response and to determine the mechanisms contributing to the inability of the host to control these infections. This knowledge will be crucial in identifying therapeutic targets for mucosal protection against the virus and co-infections.

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Previous research has highlighted the relationship between breast milk, microbiota and the developing immune system. For example, sugars in breast milk help grow specific bacteria, which in turn support certain immune cells. This new study is an important step towards understanding how these separate pieces link together and how they might influence responses to infections or vaccinations.

Similar to humans, macaques are born with virtually no T17 cells, and must develop them during the first 18 months of life. Hartigan-O’Connor and other researchers have noted that some macaques develop large T17 populations, while others have few such cells. This could profoundly affect the animals’ ability to fight infection.

To understand this variability, CNPRC investigators Hartigan-O’Connor; lead author and veterinarian Amir Ardeshir; Nicole Narayan, postdoctoral fellow; Gema Mendez-Lagares, postdoctoral fellow; Ding Lu, research scientist; and Koem Van Rompay, research scientist, with collaborating researchers from UC San Francisco followed six breast- and six bottle-fed rhesus macaques from five to 12 months of age. At six months, they found significant differences in the two groups’ microbiota; specifically, some macaques develop large T17 populations, while others have few such cells. This could profoundly affect the animals’ ability to fight infection.

Specifically, the breast-fed macaques had larger numbers of the bacteria Prevotella and Ruminococcus, while the bottle-fed group had a greater abundance of Clostridium. Overall, the microbiota in breast-fed macaques was more diverse than in the bottle-fed group, as measured by analyzing stool samples.
As I was getting ready to board my plane back from Portland after attending the annual NPRC Directors’ meeting, I was reminded of the need to take the time to give special thanks to those who make it possible for us to go about our daily lives. Alaska Airlines offers military personnel the opportunity to board first, which is obviously the right thing to do as a small token of a grateful nation’s deep appreciation for all those serving in the armed forces. I flew back on Veteran’s Day, and while this one day is the formal day of recognition to those who have served, we owe daily thanks to everyone who has served our country around the globe. To those of you in the CNPRC family who have served, or may serve now in the reserves, I want to extend a heartfelt debt of gratitude for what you do and have done for our country.

Likewise, I want to thank the entire CNPRC community for what you do for the Center on a daily basis to help make tomorrow better than today. Our shared vision of being for us is the best stewards of our nonhuman primate resource to improve human health and quality of life for both humans and animals. Those who have served in the military have sometimes had to risk their lives to liberate humanity from the tyrannies of despotism and hate, those of us not on the front lines confront tyrannies of infectious diseases, inborn genetic errors, and acquired medical conditions.

With the daily news feeds blaring constant alarmist headlines about the many challenges before us, it is sometimes difficult not to get swept up in a sense of panic. I can only imagine what it might have been like for Allied forces landing on Normandy beaches in June 1944. While the sense of the unknown, undoubtedly, must have been huge, the troops’ training and mission drove them forward to the beaches in the face of incredible odds when the ramps of landing craft lowered. One lesson we can draw from this is that the challenges in front of us today require us to keep our sense of mission and to do what we do best: use science, reason, and intellect as a collective foundation to improve human and animal health.

As we move into the holiday season, I also want to wish you and your families the very best. And, to all of those on duty around the globe and apart from their families, thanks from a very grateful nation.

**The employee of the Quarter for Summer 2014 is Kim Vanheze, Animal Technician in the Indoor Husbandry area. Kim was chosen for showing great dedication and commitment to her work here at the CNPRC. Kim continues to earn the respect and admiration of her associated through her hard work and high degree of professionalism. She is a selfless employee that volunteers for extra work and steps in where needed, helping other crews at round-up or in the hospital, uncomplainingly adding extra tasks to her already full slate of assignments. Please give Kim your congratulations!**

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**Milk, cont’d from page 1**

The surprise came when these researchers examined the immune systems of the two groups. By 12 months, the groups had significant contrasts in their immune systems, with the differences centered on T cell development. The breast-fed group showed a much larger percentage of experienced “memory” T cells that are able to secrete immune defense chemicals called “cytokines”, including Th17 cells and immune cell populations making interferon.

This is the first time researchers have shown these immunologic characteristics may be imprinted in the first few months of life. “This study suggests the gut microbiota that are present in early life may leave a durable imprint on the shape and capacity of the immune system, a programming of this system if you will,” said Ardeshir.

Further investigation suggested possible components that may drive key differences between the two groups, including arachidonic acid, which stimulates the production of Th17 cells and is found in macaque breast milk. This chemical was tightly linked to Th17 cell development and previous studies have suggested that it can influence T cell development. The researchers caution, however, that all the chemicals identified in this study must be tested in larger studies specifically designed to understand their effects.

This study also found that breast-fed infant monkeys had a higher gut microbiota diversity and richness than their formula-fed counterparts. Both Prevotella and Campylobacter were significantly more abundant in breast-fed than formula-fed animals at 12 months, and Clostridium was more abundant in the bottle-fed infants. The authors also found a network of significant correlations between stool levels of beneficial arachidonic acid, Th17 cells, and bacterial genera such as Prevotella and Campylobacter.

While this research provides a fascinating window into immune cell development in macaques, it is important to note that it does not prove the same mechanisms exist in people. While this research provides a fascinating window into immune cell development in macaques, it is important to note that it does not prove the same mechanisms exist in people.

“The team is planning similar studies in humans to test that hypothesis. In addition, this research does not prove a link between breastfeeding and better health.”

“There’s a developmental shape to the immune system that we don’t often consider,” Hartig-Tiemann said. “It’s dramatic how that came out in this study. There is a lot of variability in how both people and monkeys handle infections, in their tendency to develop autoimmune disease, and in how they respond to vaccines. This work is a good first step towards explaining these differences.”

Research projects such as these demonstrate how taxpayer dollars and donation are put to work and are leading to new diagnostics, therapeutics, and clinical procedures that enhance quality of life for both humans and animals.

**Employee of the Quarter Awards**

**From co-workers’ nominations, the CNPRC Staff Council selects exceptional CNPRC staff 4 times a year for the Employee of the Quarter (EOQ) award. We are pleased to introduce you to the 2014 Spring and Summer EOQs.**

**Deborah ‘Dee’ Tubbs, EOQ, Summer 2014**

“Dee Tubbs provides the best possible care for all of the animals in her charge. She uses her vast experience and common sense to address any challenges. The people that work with her as well as the animals are fortunate to have her as an anesthesia technician.”

**Karen Parks, EOQ, Spring 2014**

“Karen has been described by her peers as being a person of character, having a high level of expertise and confidence, and being extremely skilled in her work as chief anesthesia technician. Karen works with animals in all age groups, and has exceptional skills, knowledge, and abilities to address the needs of animals with special considerations such as neomatoes, geriatric, or titi monkeys. She assists in training staff, works on getting new equipment functioning, and providing resources to help anyone that needs assistance. Karen is a CNPRC employee who exemplifies excellence in her work.”

“**Supervisor of the Year Award**

**Inhalation Exposure Facility manager, has been named the 2014 Supervisor of the Year. Awarders are selected annually by the Director’s Office senior management team. Louise’s staff enthusiastically congratulated her on receiving this award, noting that she shows constant encouragement to think creatively “outside the box”, leading to great problem-solving. Louise has a distinctive skill to recognize that people learn in different manners, and readily adapts her training style to help her employees get the maximum benefit from training. Her enthusiasm for progress readily spreads to other members of the group, and adds to the sense of excitement about the work done at the CNPRC.**

**Staff Council:**

**Here to assist you and improve the CNPRC**

**Your Representatives are:**

Crystal Stote, Administration
Randy Bruce, Purchasing
Linda Fritts, ID Unit and CCM
Louise Olsen, Inhalation Exposure Facility

**Matt Schulte, Animal Care (Infectious)
Amanda Carpenter/Rachel DeLeon, Core
Sonia Santos, Pathology/Clinical Labs**

Tuesday Cool, Primate Medicine

**Paul-Michael Sosa, Research Services
Matt Wells, Animal Care (Tech Support)
Kari Christe, DVM, DACLAM, Inhalation Exposure Facility, Services, Infections
Justin Fontaine, Core
Gary Moore, Shop
Peter Barry, Ex officio, CNPRC Director
Clara Pacheco, Ex officio, Assistant to the Director

**Photo:** K. West

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**Photo:** S. Nishio

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**Photo:** K. West

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**Photo:** J. Janatpour

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A another successful blood drive was held at the CNPRC on August 6th, 2014. The CNPRC Staff Council and the Research Advisory Committee supported the 2nd Annual CNPRC blood drive and Paul-Michael Sosa, Research Services, worked with BloodSource to make arrangements for their visit. BloodSource depends on donors to meet patient needs in nearly 40 area hospitals in 25 counties throughout Northern and Central California (from Merced to the Oregon border and from Vacaville to Lake Tahoe). BloodSource is well-organized and very helpful in hosting these events, and Paul-Michael had over 50 people sign up to donate blood. A few last minute cancellations were easily filled with interested staff, and BloodSource has suggested they might need to bring two of their mobile units next year to be able to accommodate the incredible amount of interest in donating. Paul-Michael noted numerous staff walking around Wednesday with a white bandage around their arm, an indication that they had just donated.

Last year’s blood drive had 47 donors and 35 units of blood collected. This year’s event had an incredible turnout with 51 donors and 45 pints of blood collected. The annual event keeps growing with the strong interest and support of the CNPRC staff. As a result, Paul-Michael anticipates this will continue as a yearly event, and shares that he “is happy to see how many CNPRC staff are interested in donating, and look forward to seeing what next year will bring!”

Blood Drive, Saving Lives

Thank Goodness for Staff – Annual Event
In honor of staff

Over 230 staff from the CNPRC attended the UC Davis “Thank Goodness for Staff” event in April 2014. The annual springtime picnic and celebration is organized by UC Davis Staff Assembly to celebrate the hard work and honor the contributions of all UC Davis staff members. This signature event is attended by over 5,000 UC Davis staff members.

New Affiliate Scientists Partner With CNPRC
CNPRC Teams with Schools of Veterinary Medicine and Medicine in Faculty Recruitment

D irector Peter Barry is pleased to announce that the CNPRC has successfully partnered with the Schools of Veterinary Medicine and Medicine to recruit Dr. Sara Thomasy to the UC Davis campus. Dr. Thomasy received her B.S. in Biology from Ohio State University in 2000 and her D.V.M. from UC Davis in 2005. She then completed a Ph.D. in pharmacology and toxicology from UC Davis in 2006. Following a one-year small animal rotating internship at North Carolina State University, she completed a comparative ophthalmology residency at UC Davis in 2010. Dr. Thomasy is a Diplomate of the American College of Veterinary Ophthalmology. She will be joining the Department of Surgical and Radiological Sciences as a Professor in Comparative Ophthalmology.

The School of Veterinary Medicine Department Chair, Dr. Erik Wisner, said “the CNPRC resources and capabilities played a significant role in recruiting Dr. Thomasy to UC Davis”.

Dr Thomasy’s research interests include corneal wound healing, glaucoma, ocular pharmacology, and antiviral therapy for the management of ocular viral diseases. She is looking forward to an active research program at the CNPRC and collaborating with Core Scientists in several areas of nonhuman primate research.

“Saving Lives

Developing new strategies to treat blinding eye diseases

A nna La Torre, Ph.D., recently joined UC Davis as an Assistant Professor in the Department of Cell Biology and Human Anatomy, School of Medicine, and as a new member of the UC Davis vision science community. Dr. La Torre completed her Ph.D. in neurobiology in 2008 at the University of Barcelona in the laboratory of Dr. Eduardo Soriano, and a postdoctoral fellowship with Dr. Thomas Reh at the University of Washington in 2013. She is a member of the Society for Developmental Biology and the Association for Research in Vision and Ophthalmology.

One of the primary goals of Dr. La Torre’s research is to understand how cone photoreceptors are generated during development in order to devise new cellular strategies to treat blinding eye diseases in humans, including age-related macular degeneration. It is known that in primates a region of the central retina, the macula, has the highest density of cone photoreceptors. The macula is responsible for most of vision under well-lit conditions, and once cone photoreceptors have degenerated the only means to restore vision is with cell replacement. Dr. La Torre has developed a protocol to differentiate pluripotent cells to retinal fates, including photoreceptors. She plans to systematically characterize gene expression profiles in the developing macula in the rhesus monkey in order to fully understand the mechanisms of cone photoreceptor differentiation, and to develop new approaches for the differentiation of pluripotent cells towards the desired retinal lineages. Dr. La Torre will be working with Dr. Alice Tarantal in the Reproductive Sciences and Regenerative Medicine Unit at the Primate Center, including collaborating on new NIH grant submissions and other funding opportunities.

Dr. La Torre was recently named a Center for the Advancement of Multicultural Perspectives on Science (CAMPOS) faculty scholar through the UC Davis ADVANCE program (http://ucd-advance.ucdavis.edu/). This program is supported by the National Science Foundation and aims to increase the participation and advancement of women in academic science and engineering careers.
UC Davis Affiliate Joins CNPRC Scientific Team

Haczku to work with Respiratory Diseases Unit in the new Respiratory Disease Center

We are honored to have Angela Haczku, M.D., Ph.D., joining the CNPRC as an Affiliate Scientist. Dr. Haczku is a Professor of Medicine and Director of the Translational Lung Biology Center at the Pulmonary, Critical Care and Sleep Medicine Division, UC Davis. She was trained in internal and pulmonary medicine at the University of Debrecen, Hungary, and obtained a Ph.D. at the Imperial College, London, UK, completing her post-doctoral training in immunology at the National Jewish Medical and Research Center, Denver, Colorado. She studies the effects of environmental exposures on lung biology, and is internationally recognized as an expert in pulmonary immunity, innate immunity and experimental modeling of lung inflammation. Her group was one of the few that raised the immunoprotective significance of surfactant proteins A and D in allergen and ozone induced airway inflammation and the first one that described a negative feedback regulation between these lung collects and pro-inflammatory processes. Her team recently established a unique murine model to study the effects of environmental exposures on lung function.

Frequently a member of NIH study sections, Dr. Haczku most recently completed a standing membership in the Lung Cellular, Molecular, and Immunobiology study section as well as serving on the VA Respiratory Merit Review Awards Board. She serves at the American Academy of Asthma, Allergy and Immunology as an Annual Meeting Program Committee member and chairs the Workshops Committee. She also served on the American Thoracic Society (ATS) Scientific Advisory Board, the ATS/AIIN Nominating and Planning Committees and is currently the Program Committee Chair-elect.

Dr. Haczku believes that the key to excellence lies in the ability to train and inspire the next generation of researchers. She aims to facilitate the participation of outstanding UC Davis basic scientists in pulmonary research and to increase the opportunities for Ph.D. and clinical researchers to interact.

Dr. Haczku studies the effects of environmental exposures on lung biology, and is internationally recognized as an expert in pulmonary immunity, innate immunity and experimental modeling of lung inflammation.

Along with her postdoctoral fellow Moyar Ge, Dr. Haczku has moved into the new Respiratory Disease Center and will work closely with Respiratory Diseases Unit Core Scientists Lisa Miller and Ed Schelegle on asthma studies. Dr. Haczku has also recently collaborated with Brain, Mind, and Behavior Unit Core Scientist John Capitanio in the submission of an NIH proposal to evaluate the mechanisms of stress and asthma.

Recycling gravel will save $40,000 a year compared to the costs of landfilling it and buying replacement gravel.
Spotlight on Services

The UC Davis – CNPRC partnership for growth of the research enterprise represents an unprecedented commitment of resources to a long-term vision of CNPRC-initiated research that addresses the medical challenges that face the world today and that will continue to arise in the future. UC Davis has been working towards a transformational level of improvement to our physical plant. It is exciting to see the high level of support we are receiving in grounds and landscape beautification around the Center. Trees and shrubs have been manicured, lawns and grass clipping have been removed, and many of the shrub beds located throughout the CNPRC grounds have been mulched.

Parking services has also been working to provide the Center with a lower cost parking option in a gravel lot to the north of the administration building. We are hoping to have this new parking option available by the first of the new year, and will keep everyone informed on the progress of this project and how to purchase a permit for this area.

Campus facilities crews have and will continue to be working indoors as well as general maintenance and painting projects. We have received a significant commitment from our campus facilities colleagues to invest in the highest priority deferred maintenance projects that we have asked them to address.

Following are a few other examples of UC Davis and CNPRC teamwork and mutual commitment to advancing our mission and each of us can be proud of our individual and collective contributions!

• New Faculty Positions. The campus has made an exceptional promise of 10 full faculty positions as part of the CNPRC director recruitment. These positions are essential to our long-term growth, and the faculty will be located within five Schools and Colleges (Medicine, Veterinary Medicine, Engineering, Biological Sciences, and Letters and Science).

• Participation of Campus Leadership During the Upcoming NIH Site Visit. The Chancellor, Provost, Vice Chancellor for Research, and the five Deans (or their representatives for those unavailable) will be on hand on the morning of the site visit to speak briefly to the reviewers about the campus’ commitment to the CNPRC.

• STARS Award. The UC Davis campus applied for and was awarded a Strategic Teaching Acquisition and Retention (STARS) award from the Office of the President as part of the recruitment package for the new director. This $6.6M award is an interest-free loan from the Office of the President that will provide new resources to faculty recruitment in the next several years. This award is a powerful statement of the dedication of the campus and University of California to the long-term mission of the CNPRC.

The enhancements to the CNPRC physical plant and work environments and dedication to our research programs are clear examples of the UC Davis campus administration’s support of the significant impact that our collective efforts have on advancing human and animal health. It is clear that the CNPRC is a valued and integral component of the UC Davis biomedical research mission and each of us can be proud of our individual and collective contributions!

New signage has been produced by campus to demonstrate to our visitors the close collaborative ties to UC Davis. The image chosen is of a sculpture depicting monkeys at a temple in India. The story behind the sculpture has a number of ties with our mission here at the CNPRC – respect, perseverance, strength and service. Look for a plaque in the lobby with the story behind the image.

Photo by: Photo Dharma, Flickr

Decades of Service to the Scientific Community

Pathogen Detection celebrates 30th anniversary of publication

Thirty years ago the CNPRC was at the forefront of discovering the role of retroviruses as the causative agent for Acquired Immunodeficiency Syndrome (AIDS). Dr. Murray Gardner, emeritus Professor of Pathology at the UC Davis School of Medicine, often refers to the CNPRC as the “home” of simian AIDS, as early isolates of retroviruses related to human immunodeficiency virus (HIV) were identified in colony animals and studied by researchers here.

In 1982, the late Nicholas Lerche, D.V.M., M.P.V.M., applied his expertise in epidemiology to investigate an unusual outbreak of immune deficiency that was occurring in a population of chimp monkeys housed in outdoor corrals. In a series of elegant studies first published in 1984, Dr. Lerche demonstrated that this immune deficiency disorder was the result of an infectious agent and spread by direct contact. The subsequent discovery and characterization of Simian Retrovirus (SRV) by Dr. Lerche and CNPRC colleagues led to the identification of another retrovirus, Simian Immunodeficiency Virus (SIV). The report of SIV was fortuitous in its timing, occurring almost exactly at the same time as HIV was causing disease of unknown origins around the world. SIV infection in macaque monkeys became the critically important animal model for studying HIV infection in humans, leading to new discoveries and treatments for HIV/AIDS.

The Pathogen Detection laboratory (PDL) emerged from this early period of retrovirus discovery. In 1985, before there were commercial tests on the market, PDL originated as the AIDS Virus Diagnostic Laboratory, founded to develop and provide one of the only testing facilities for the newly discovered public health threat – HIV. The laboratory began by resurrecting an abandoned research building on the outskirts of campus, sandwiched between the railroad tracks and the cat barn. This new laboratory provided serology and culture results for researchers, blood banks, public health, reference and hospital laboratories, and private physicians across the country. In 1987 the AIDS Virus Diagnostic Laboratory expanded its services to provide virus testing for nonhuman primates in support of animal models for HIV research. The laboratory played a major role in ensuring CNPRC animals remained healthy by monitoring the eradication of SRV, SIV and Simian T-cell Leukemia Virus (STLV) from the Center’s monkey colonies.

Dr. Michael Lairmore, Dean of the UC Davis School of Veterinary Medicine, was one of the lab’s early collaborators on STLV testing. As diagnostic kits for HIV became commercially available and the need for nonhuman primate testing increased, JoAnn Yee, one of the founding staff members from the AIDS Virus Diagnostic Laboratory, began working with Dr. Lerche in the newly formed Simian Retrovirus Reference Laboratory (SRRL). At its peak, SRRL processed over 10,000 samples from more than 100 clients for up to half a dozen different agents each year. With growth and expansion of testing for other pathogens identified in nonhuman primates, SRRL underwent a name change to Pathogen Detection Laboratory. The Pathogen Detection resource recently became part of a larger effort in immunology and pathogen detection, as a key component of the Immunology and Pathogen Detection Resources Core.

The legacy of Dr. Lerche’s scientific contributions to pathogen detection remains today. Pathogen Detection Resources continues to offer testing, but the focus has expanded to providing training, proficiency testing, troubleshooting, reagents, controls, and protocols. The staff’s extensive experience in resolving problem cases is a key factor in their ability to develop new assays and provides a unique service not available in other laboratories.

In 1987 the AIDS Virus Diagnostic Laboratory expanded its services to identify antibodies against human immunodeficiency virus (HIV) in nonhuman primate specimens. The laboratory played a major role in ensuring CNPRC animals remained healthy by monitoring the


**Out & About**

**Conferences and Symposia**

CRISP 14.2, November 2014


Dr. Tamara Weinstein, Assistant Project Scientist, gave an invited presentation at the International Behavioral Neuroscience Society in Las Vegas, Nevada, June 10–15, 2014, entitled “Neural Correlates of Social Separation During Exposure to an Acute Stressor: Companion Identity Matters.”

Dr. Sara M. Freeman, postdoctoral fellow, gave a poster presentation at the Collaborative Biomedical Research Conference on the Vole Animal Model, July 25–26, 2014, in Portland, Oregon, Oregon Health and Science University entitled “The Neuroanatomical Structure of Silent-bared-teeth Display Networks in Captive Groups of Laboratory-housed Coppery Titi Monkeys (Callicebus cupreus);” and at the ZIF Conference on Adaptive Behavioral Activation, Florence, Italy, April 5–9, 2014, entitled “Social Separation Affects Affiliation in the Titi Monkey: Relevance to Social Deficits and Autism.”

Dr. Linda B. Winder, Ph.D., postdoctoral fellow, gave a poster presentation entitled “Evidence of convergent infection in humans and rhesus macaques.”


Dr. Melissa Bauman gave an oral presentation entitled “Validation of a Partner Preference Test in Coppery Titi Monkeys (Callicebus cupreus);” and at the ZIF Conference on Adaptive Behavioral Activation, Florence, Italy, April 5–9, 2014, entitled “The Brain, Mind, and Behavior Unit was well-represented at the American Society of Primatologists (ASP) meetings, September 12–15, 2014, in Decatur, Georgia;”

Dr. Karen Bales gave an invited talk entitled: “‘Unusual’ Animal Models: the Role of Social Environment and Early Experience in Healthy Aging;”

Dr. Brianne Beisner, postdoctoral fellow, presented a poster entitled “Receipt of Silent-Bared-Teeth Signals in Peaceful Contexts Predicts Conflict Policing Behavior in the Titi Monkey.”

Dr. Emily S. Rothwell, graduate student, presented a poster entitled “Continuing Oxytocin Treatment into Adulthood Does Not Ameliorate Social Deficits in Rhesus Monkeys (Macaca mulatta)”.

Dr. Dan Kimmel gave a talk at the Collaborative Biomedical Research Conference on the Vole Animal Model, July 25–26, 2014, in Portland, Oregon, Oregon Health and Science University entitled “Continuing Oxytocin Treatment into Adulthood Does Not Ameliorate Social Deficits in Rhesus Monkeys (Macaca mulatta).”


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‘Surprised and Honored,’ First recipient of special award

Jeffery Roberts, D.V.M., Associate Director of Primate Services, was honored to become the first recipient of the Nicholas W. Lerche award, at the Association of Primate Veterinarians (APV) workshop held October 15–18, 2014, in San Antonio, Texas. This award is especially meaningful to Dr. Roberts, as Dr. Lerche was a longtime colleague, mentor, and friend. Dr. Roberts was chosen as the inaugural recipient of this award for his outstanding contributions to improving the field of primate medicine.

The Nicholas W. Lerche Award was established to recognize members of APV who exemplify one or more of the talents that made Dr. Lerche an honored member of APV. He was an epidemiologist, researcher, clinician, and mentor to veterinary and graduate students, and dedicated to improving the field of medical primatology by understanding infectious diseases and developing methods to prevent transmission in captive primate colonies. Above all, he was the ideal colleague, openly sharing his knowledge with fellow scientists and clinicians and answering questions freely. His intellect, generosity, and commitment to science serves as a model to all individuals in the field of medical primatology.

Infectious Diseases Unit

 Connecting with the Community

As a busy director of both the CNPRC and the Center for Comparative Medicine, Dr. Peter Barry makes time in his hectic schedule to maintain an active role in his program in cytomegalovirus (CMV). He recently took time to make a personal connection with an individual from the public that has first-hand experience with CMV and is looking to us to speed the discovery of a vaccine and treatment to human trials and general use in human medicine. Following is Barry’s thoughtful response to this urgent request, October 9, 2014.

“I am writing you regarding your inquiry regarding the Cytomegalovirus (CMV) vaccine research article. I was the lead scientist on the study described in this article, and I want to personally update you on the current status of the research, particularly in light of your having had the extremely unfortunate experience of suffering from CMV disease. The article describes ongoing research by my lab in developing a vaccine that can prevent both CMV infection and CMV disease.

By way of background, intensive efforts to develop a vaccine against CMV have been ongoing for more than 40 years. The clinical consequences of CMV infection and disease in at-risk individuals were first recognized more than 100 years ago, and CMV has long been recognized as a significant infectious threat in particular groups of individuals, notably in immunosuppressed transplant recipients and fetuses who acquire virus from their mother during pregnancy. In addition, CMV can occasionally cause disease in individuals apart from these groups, such as yourself. While scientists have been highly successful in developing vaccines against many viruses and bacteria that have long plagued humankind (polio, smallpox, measles, diphtheria, pertussis, to name a few), other infectious agents present major challenges, including CMV. Other challenges include developing vaccines for tuberculosis, malaria, and HIV. Despite some of the best minds in the world working on these pathogens, we are not yet at the point where these pathogens can recede into the history books.

The CMV vaccine effort described in the article is work from my lab in which we are trying to develop a completely novel vaccine against CMV by targeting what we believe is an especially vulnerable part of the virus. The work is experimental at this point. While we have made great progress in our animal models, we still need to conduct more experiments in animals before we advance the studies to human clinical trials. While the progress may seem frustratingly slow to you and others who know from first-hand experience the pain and consequences of CMV disease, I want to assure you that we are working as hard and as fast as we can. Our goal is to get it right. The costs and challenges in conducting human clinical trials are enormous, and our goal is to demonstrate in our animal models that we can eliminate as many unknowns before we advance the work to people.

I also want to emphasize that our research is an example of Americans’ taxes and donations at work. My research, and that of almost all researchers in the U.S., is funded through grants awarded by the National Institutes of Health, which is allocated monies through the annual budgetary process of Congressional allocation and the signature of the President. We take this fiduciary responsibility very seriously, and I can speak for the countless other researchers across the country when I assure you that we are absolutely committed to the mission of using these funds in the most cost-effective and efficient manner to advance human health and well-being.

I am not a clinician, and therefore, not in a position to address specific medical issues related to your disease or the potential for CMV activation. As a basic scientist, however, I can tell you that, in general, CMV infection stimulates the immune system to develop long-term immune responses that prevent CMV disease in the future. While this is not necessarily a guarantee for you, there are many clinicians and scientists working diligently so that you and others never have to experience CMV again.

I wish you all the very best, and please feel free to ask questions. If I don’t have an answer, I will find someone who does.

Sincerely,
Peter Barry


‘For myself and the thousands of people your research efforts may someday impact I want to thank you and wish you the best.’ Jim, CMV patient

UC Davis Honors
Most accomplished investigator

Dr. Alice Tarantal, Reproductive Sciences and Cell Biology, University of California, Davis, 2014 UC Davis School of Medicine Research Award. The nominating faculty member describes her as “one of UC Davis’ most accomplished investigators. Period. Alice has earned literally scores of research grants totaling tens of millions of dollars in just the last few years. This should constitute the overwhelming independent evaluation of her research reputation at the national and state levels.”

Dr. Tarantal’s research program includes the following areas of nonhuman primate translational research: gene therapy, stem cell therapies, regenerative medicine, pediatric models of human disease, and translational in vivo imaging technologies.

Robert L. Lerche, D.V.M., Core Scientist and Unit Leader, and Professor of Pediatrics and Cell Biology and Human Anatomy, received the 2014 UC Davis School of Medicine Research Award. The nominating faculty member describes her as “one of UC Davis’ most accomplished investigators. Period. Alice has earned literally scores of research grants totaling tens of millions of dollars in just the last few years. This should constitute the overwhelming independent evaluation of her research reputation at the national and state levels.”

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Students, Staff and Faculty Earn Accolades

• After years of preparation and a grueling exam, Dr. Marie Josee Lemoyn, CNPRC veterinarian, is now a Diplomate of the American College of Laboratory Animal Medicine (August 1, 2014).

• The publication “Persistence of Serotonergic Enhancement of Airway Response in a Model of Childhood Asthma” with lead author Brian D. Moore, who recently completed his Ph.D. in the Respiratory Diseases Unit, was selected to be a highlighted junior investigator publication for the July 2014 issue of the American Journal of Respiratory Cell and Molecular Biology.

• Dr. Melissa Bauman, CNPRC Affiliate Scientist and UC Davis Assistant Professor, Department of Psychiatry has had an abstract accepted for inclusion in Society for Neuroscience 2014’s ‘Hot Topics’ book. Her abstract is entitled: “Cortical Inflammation and Increased Pre-synaptic Serotonin Dopamine in a Nonhuman Primate Model of Maternal Immune Activation”.

• Emily S. Rothwell, graduate student in the Brain, Mind, and Behavior Unit, has received a two-year award (July 2014 – June 2016) for training-related and fees/tuition expenses from the Bay Area Predoctoral Training Consortium in Affective Science, National Institute of Mental Health.

• Sarah Carp, a UC Davis ADVANCE Scholar and CNPRC staff in Brain, Mind, and Behavior received a Dakes Fund Travel award in March 2014 from the UC Davis Psychology department.

• Dr. Katie Hinde, Affiliate Scientist and Assistant Professor in Human Evolutionary Biology at Harvard University, was the first recipient of the American Society of Primatologists Early Career Award, September 2014.

‘Highest Honors

Affiliate Scientist recognized

CNPRC Affiliate Scientist Dr. Carol Barnes, University of Arizona, was recently recognized as a recipient of one of the highest honors for scientific achievement by psychologists, the 2014 American Psychological Association Distinguished Scientific Awards. Dr. Barnes was recognized for her groundbreaking work on the neurobiological mechanisms underlying memory changes in normal aging, which showed that uncovering the potential background against which disease-related brain changes can be understood. http://www.apa.org/science/about/psa/2014/05/distinguished-scientific-awards.aspx
Research Highlights

Reproductive Sciences and Regenerative Medicine
Collaborative Opportunities, Services, and Training in Regenerative Medicine and Gene Therapy

Core Scientists in the Reproductive Sciences and Regenerative Medicine at the CNPRC mission through a range of collaborative opportunities and services to the greater research community, and by mentoring all trainees. The CNPRC researchers have been instrumental in the initiation of a human clinical trial of adeno-associated virus (AAV) gene therapy in Pompe disease in infants, and the results of this and a related study with in vivo imaging to monitor gene expression were a component of an IND submission for the use of AAV in 3- to 14-year-old patients who have developed ventilator dependence (Smith et al., 2013). For these studies, each aspect of the clinical development plan was facilitated by the NHLBI Center thus overcoming regulatory barriers. The landmark study, each one characterizing novel mouse models of the disease, was challenging, and the NHLBI Center is a crucial component in successfully addressing this important process. A current ongoing study will further help in defining the ideal AAV dose range to support a new clinical trial in infants with Pompe disease.

Any investigator funded by the NHLBI is eligible to submit an application to the program, and those supported by other NIH institutes can also submit applications if funds are provided by their funding agency. The call for proposals is circulated annually; posted on the NHLBI website under Resources as well as on the NHLBI Center, CNPRC, and American Society of Gene and Cell Therapy websites; presented at national meetings; and published in the May issue of the journal Molecular Therapy. Full applications are requested after review and approval of submitted Letters of Intent, and projects are selected by a standing External Advisory Committee composed of leaders in the field. The program also routinely provides cells, tissues sections, RNA, and DNA to investigators nationwide upon request throughout the calendar year.

Linked with the Center is the NHLBI Annual Gene Therapy Symposium for Heart, Lung, and Blood Diseases, currently in the 13th year (www.GTS.acudavis.edu). The intent of these annual multidisciplinary symposia is to provide a novel and informal scientific setting for the dissemination and exchange of new ideas and research findings by bringing together trainees and investigators that do not typically interact at other meetings. Students and fellows are supported through a competitive process and have the opportunity to present their research in a brief oral presentation followed by a poster session, and interact with leading scientists in the gene therapy and regenerative medicine fields.

With the CNPRC-wide focus on lifespan health, these ongoing collaborative partnerships and research, training, and service opportunities also address bottlenecks to improving human health and healthy aging.


Primate Models in Research

In this review, scientists discuss the importance of primate models for advancing knowledge in biomedical and biological research. Presenting an honest, forthright discussion of the pros and cons of using nonhuman primates (NHP) in research, and demonstrating the vital role NHP have played in many of the medical and scientific advancements of the past century, 14 scientists, including CNPRC researchers Drs. Karen Bales, John Capitanio, and Lisa Miller, published a collaborative review article in the American J. of Primatology entitled “Why Primate Models Matter” on April 15, 2013 (EarlyView).

The Neurobiology of Love

The Neurobiology of Love: https://studiesoflove.org

On Feb. 11, Dr. Sarah Strand, Staff Research Associate in the Brain, Mind, and Behavior Unit, updated and expanded on her talk about the research around the neurobiology of love on the Sacramento public radio station, Capital Public Radio. “We’re talking to Dr. Strand to gain a deeper understanding of how love works in our brains and why it’s important.”

Sarah did an excellent job making complex science accessible and fun, and representing the CNPRC. Congratulations, Sarah, on a great interview!

Monkeys, Milk and Comedians


Dr. Krat Hinde, CNPRC Affiliate Scientist, was interviewed by three comedians, Eugene Mirman, Sarahowell, and Wyatt Cenac, to learn about her research. Listen to a hilarious, interesting and informative interview.

Learn about the science and capabilities at the CNPRC and other primate centers

Two dynamic new websites were recently released to provide expanded outreach to research collaborators. The CNPRC’s newly designed website went live in the summer of 2014 (cnprc.ucdavis.edu). Please visit the site and enjoy reading about the extensive information and resources available to educate the public and to inform collaborators. The CNPRC also has a Facebook page (California National Primate Research Center) and Twitter account (California CNPRC), “tweeting” and follow recent news from the Center. These are also great resources to share with your friends, family and colleagues.

The NPrC Consortium has recently launched a new website that is an informative resource to help facilitate innovative research with nonhuman primates: NPRCResearch.org. The new website is designed to help investigators determine which NPRCs provide the necessary expertise and resources to help the investigator with their studies, and to identify collaborative scientists at the NPRCs who can provide guidance on the use of nonhuman primate models and assays.
Loneliness and health
from the University of Chicago, and Dr. Steven Cole from
in Humans and Rhesus Monkeys (Macaca mulatta)"
others – just like in humans" emphasizes Dr. Capitanio.
induced models – for example an animal is physically
found a subset of animals with low social engagement
monkeys in their social groups at the CNPRC, Dr. Capitanio
behavioral consequences when there is a disconnect between
that was the focus of a research study by John Capitanio,
engage with others. It is the choice of sociality, and the
of desire to be social. Some prefer to be alone rather than
some physiological reasons for improved health and disease
However, not all people, nor animals, have the same level
social desire to be social. Some prefer to be alone rather than
either model, that is, they choose differently to the animals
Dr. Capitanio
University of Chicago; Drs. Allan Jobe and Suhas
Jobe is a professor in the Department of Pediatrics at the University of Cincinnati and
Department of Pediatrics at the University of Cincinnati and
Department of Pediatrics at the University of Cincinnati and
CNPRC Core Scientists Lisa Miller, Ph.D., Respiratory Disease Unit Leader and Alice Tarantal,
CNPRC Reproductive Sciences and Regenerative Medicine Unit Leader, on research at the CNPRC in the pathogenic effects of chorioamnionitis on the fetal immune system. Very low birth weight preterm newborns who are susceptible to the development of debilitating inflammatory diseases, many of which are associated with chorioamnionitis.
It had been previously thought that chorioamnionitis events leading to preterm labor were due to infectious colonization
Out & About, cont’d from pg 7
Representing the Respiratory Diseases (RD) Unit: Dr. Lisa Miller, RD Unit Leader attended the American Thoracic Society Meeting in San Diego, California May 17–21, 2014 along with Dr. Candace Burbke and Dr. Black participated in poster discussion sessions with the following abstract titles: “Wildfire Smoke Exposure During Infancy Results in Constitutive Attenuation of Transcription Factor and Signaling Gene Expression Associated with the Toll Like Receptor Pathway in Adults” (Black), and “Exogenous IL-12 Therapy During Infancy Results in Exacerbation of the Asthma Phenotype: Mechanisms of Airways Eosinophilia and Monocyte Interferon Gamma Production” (Burbke).
Dr. Miller also gave a seminar entitled “The Intersection of Environment and Immunity During Life: Lessons Learned from the Nonhuman Primate” at the National Jewish Hospital in Denver, Colorado, April 2014, and a seminar entitled “The Intersection of Environment and Immunity During Life: Lessons Learned from the Nonhuman Primate” at the Medical Microbiology Seminar Series, UC Davis, March 2014.
Dr. Candice Clay, postdoctoral fellow, gave a talk at the Fifth Annual UC Davis Lung Research Day on May 7, 2014. Her talk was entitled "New Insights into Influenza"
Loneliness and health

from the University of Chicago, and Dr. Steven Cole from UCLA. The research, which also includes studies with humans, was supported by the National Institute on Aging.

First using a sample of older adult humans, the psychologists examined how loneliness was influenced both by social network size and by the extent to which individuals believed that their daily social interactions reflected their own choice. As expected, the study showed that loneliness was highest among individuals who have low levels of social interaction, but who may be dissatisfied with those levels (low choice in determining those levels); in fact, individuals with comparably sized social networks, but who indicated that their amount of social interaction reflected their own choice (previously reflecting satisfaction with their level of interaction), reported significantly less loneliness. Put another way, people who are lonely show a discrepancy between their social interest and social attainment.

As the second step in this study, Dr. Capitanio and colleagues sought to determine whether a similar classification might also hold true for macaques. Dr. Capitanio borrowed the Macaque Taxonomy of Loneliness (MaTOL), the first animal model to classify individuals, also known as Macaca mulatta," emphasizes Dr. Capitanio.

"Importantly, our study describes a naturally occurring animal model to understand the behavioral and biological 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, Ph.D., Core Scientist in the Brain, Mind, and Behavior Unit at the CNPRC.

There is no fundamental reason that this perception of social disconnection, or loneliness, might be specific to humans. Rhesus monkeys, for example, are a highly social nonhuman primate species. Observing adult male rhesus monkeys in their social groups at the CNPRC, Dr. Capitanio found a subset of animals with low social engagement that seem to want more interaction than they have. This study demonstrated that this species could serve as a useful model to help us understand the behavioral and biological consequences of loneliness.

"Our results demonstrate that nonhuman primates may provide a valuable animal model to better understand how chronic loneliness contributes to poor health as people age."

Together, the 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. More about Dr. Capitanio’s research and publications can be found at www.cnprc.ucdavis.edu/John-P-Capitanio/.

Research highlights

Respiratory Diseases

Understanding the fetal inflammatory response

Many Allied Scientists come to the CNPRC to conduct research that is crucial to human health and well-being, including Drs. Allan Jobe and Suhas Kallapur from the University of California, San Diego, and Dr. Mark Miller, Ph.D., Respiratory Disease Unit Leader and Alice Tarantal, CNPRC Reproductive Sciences and Regenerative Medicine Unit Leader, on research at the CNPRC to the pathogenic effects of chorioamnionitis on the fetal immune system. Very low birth weight premature neonates are susceptible to the development of debilitating inflammatory diseases, many of which are associated with chorioamnionitis.

It had been previously thought that chorioamnionitis events leading to preterm labor were due to infectious colonization of the endometrium, leading to diffuse invasion of the chorioamnion and amnion prior to spreading into the amniotic fluid and fetus. However, more recent studies support a different model of infection of the chorioamnion with spread into the amniotic fluid and the fetus prior to the development of diffuse chorioamnionitis. This distinction in the pathways leading to infection and inflammation of the fetal compartment is important as it changes the direction of pro-inflammatory signal for preterm labor from the uterus to the fetal compartment.

This collaboration between Allied Scientists and CNPRC Core Scientists provided the first experimental evidence that a chorioamnionitis-induced interleukin axis is involved in the severe inflammation that can develop in preterm newborns.

Their results indicated that a chorioamnionitis-induced IL-1β/IL-17 axis is involved in the inflammation developing in very preterm newborns. The capacity of fetuses to mount a robust IL-17 response might constitute a double-edged sword, as it would afford them protection against infections by bacteria and fungus, but could also play a role in the development of devastating inflammatory disorders often seen in the very preterm babies. Findings from this study also suggest that boosting Treg cells, which modulate the immune system, and/or modulating IL-1β/IL-17 axis could provide a therapeutic avenue to manage the pathogenesis of chorioamnionitis.

Overall, this study clearly demonstrated that the fetal rhesus macaque is a suitable animal model to study mechanisms of inflammation during human fetal development.

Out & About, cont’d from pg 7

Representing the Respiratory Diseases (RD) Unit: Dr. Lisa Miller, RD Unit Leader attended the American Thoracic Society Meeting in San Diego, California May 17–21, 2014 along with Dr. Candace Burke, CNPRC Respiratory Disease Unit Leader and postdoctoral fellow Burke and Black participated in poster discussion sessions with the following abstract titles: “Wildfire Smoke Exposure During Infancy Results in Corticosteroid Resistance of Transcription Factor and Signaling Genes Associated with the Toll Like Receptor Pathway in Adults” (Black), and “Exogenous IL-1/Therapy During Infancy Results in Exacerbation of the Asthma Phenotype: Mechanisms of Airways Eosinophilia and Monocyte Interferon Gamma Production (Burke).”


Dr. Miller also gave a seminar entitled “The Intersection of Environmental Medicine and Community Based: Lessons Learned from the Nonhuman Primate” at the National Jewish Hospital in Denver, Colorado, April 2014, and a seminar entitled “The Intersection of Environmental Medicine and Community Based: Lessons Learned from the Nonhuman Primate” at the Medical Microbiology Seminar Series, UC Davis, March 2014.

Dr. Candice Clay, postdoctoral fellow, gave a talk at the Fifth Annual UC Davis Lung Research Day on May 7, 2014. Her talk was entitled “New Insights into Influenza”.
Reproductive Sciences and Collaborative Opportunities, Services, and Training in Regenerative Medicine and Gene Therapy

C
ore Scientists in the Reproductive Sciences and Regenerative Medicine programs at the CNPRC have championed a mission through a range of collaborative opportunities and services to the greater research community, and by mentoring all trainees. The CNPRC’s unique collaborative opportunities are essential in successfully addressing important processes and by facilitating the leap from preclinical discovery to human subjects research, which can lead to death due to impaired muscle contractility which can lead to death due to impaired respiratory insufficiency in pediatric patients. Byrne BJ. Phase I/II trial of adeno-associated virus-mediated alpha-glucosidase gene therapy to the diaphragm for chronic respiratory failure in Pompe disease: initial safety and ventilatory outcomes. 

Pompe disease is an autosomal recessive disorder caused by severely reduced or absent alpha-glucosidase activity (GAA). The use of AA V in rhesus monkey muscle, and the results of this and a related study with in vivo imaging to monitor gene expression were a component of an IND submission for the use of AA V in 3- to 14-year-old patients who had developed ventilator dependence (Smith et al., 2013). For these studies, each aspect of the clinical development plan was facilitated by the NHLBI Center through a range of collaborative opportunities and services that are provided nationwide to investigators is through the National Heart, Lung, and Blood Institute (NHLBI)-supported Center for Fetal Monkey Gene Therapy. Registered in Vietnam, the NHLBI Center serves a crucial role in the research community by addressing questions of using nonhuman primates (NHP) in research, and demonstrating the vital role of NHPs in advancing the field of human health and healthy aging. 

In many ways, Blash-Moreau looks like a perfect candidate. This year, she won a K99 postdoctoral fellowship from the National Institute of Mental Health, the first half of the prestigious K99/R00 transition award, and she is pursuing cutting-edge questions at the boundary between disciplines, to leap out the biological and social mechanisms that underlie emotion, she uses a range of theory and experimental methods from social psychology to physiology. Her most recent workraads on imaging of monkeys' brains. 

Established in 2001, this program is unique to the CNPRC and provides investigators nationwide with opportunities to test new vector constructs and cell transplant approaches that advance the field. The NHLBI Center has conducted over 40 collaborative projects for investigators across the research institutions such as: Beckman Research Institute at the City of Hope, Children’s Hospital Los Angeles, George Washington University, Harvard University, St. Jude Children’s Research Hospital, Stanford University, UCLA, UCSF, University of Florida, University of North Carolina, University of Pennsylvania, and Washington University in St. Louis, to name a few. The established infrastructure and expertise in the program can rapidly design and test new paradigms, map new hypotheses and emerging gene transfer vectors into a preclinical setting, and provide critical preliminary data for new NIH grants and investigational new drug (IND) submissions for the Food and Drug Administration (FDA). Examples include new treatments for pediatric disorders such as Pompe disease, adenosine deaminase deficiency, were combined immunodeficiency, and Duchenne muscular dystrophy.

Ongoing studies with Dr. Barry Byrne, University of Florida, have been instrumental in the initiation of a human clinical trial to correct respiratory insufficiency in pediatric patients with Pompe disease (clinical identifier: NCT00976352). Pompe disease is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme, alpha-glucosidase (GAA). Severely reduced or absent GAA activity results in glycogen accumulation, particularly in muscle, reducing muscle contractility which can lead to death due to impaired cardiac and respiratory function. A series of studies conducted in the NHLBI Center were essential in achieving the overall goal of utilizing adeno-associated virus (AAV) expression of human GAA in Pompe patients. Initial studies established the utility of AAV in a mouse model of Pompe disease, and the results of this and a related study with in vivo imaging to monitor gene expression were a component of an IND submission for the use of AAV in 3- to 14-year-old patients who had developed ventilator dependence (Smith et al., 2013). For these studies, each aspect of the clinical development plan was facilitated by the NHLBI Center through a range of collaborative opportunities and services that are provided nationwide to investigators is through the National Heart, Lung, and Blood Institute (NHLBI)-supported Center for Fetal Monkey Gene Therapy.

In 2011, Dr. Sarah Strand, Brain, Mind, and Behavior Unit, updated and expanded on her talk about the research around the neurobiology of love on the Sacramental public radio station ‘Capital Public Radio’. “We’re talking to Dr. Strand to gain a deeper understanding of how love works in our brains and why it’s important.”

Sarah did an excellent job making complex science accessible and fun, and representing the CNPRC. Congratulations, Sarah, on a great interview!

Monkeys, Milk and Comedians

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Monkeys, Milk and the NY Times

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The Neurobiology of Love

‘Primate Models in Research’

The Romanian Orphanage Model of Ankylosing Spondylitis

‘Primate Models in Research’

The Neurobiology of Love: http://ia601206.us.archive.org/15/items/Insight-140214/Insight-140214b.mp3

The Neurobiology of Love

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The Neurobiology of Love
**Infectious Diseases Unit**

**Connecting with the Community**

As a busy director of both the CNPRC and the Center for Comparative Medicine, Dr. Peter Barry makes time in his hectic schedule to maintain an active engagement program in cytomegalovirus (CMV). He recently took time to make a personal connection with an individual from the public that has first-hand experience with CMV and is looking to us to speed the discovery of a vaccine and treatment to human trials and general use in human medicine. Following is Barry’s thoughtful response to this urgent request, October 9, 2014.

“I am writing you regarding your inquiry regarding the Cytomegalovirus (CMV) vaccine research article. I was the lead scientist on the study described in this article, and I want to personally update you on the current status of the research, particularly in light of your having had the extremely unfortunate experience of suffering from CMV disease. The article describes ongoing research by my lab in developing a vaccine that can prevent both CMV infection and CMV disease.

By way of background, intensive efforts to develop a vaccine against CMV have been ongoing for more than 40 years. The clinical consequences of CMV infection and disease in at-risk individuals were first recognized more than 100 years ago, and CMV has long been recognized as a significant infectious threat in particular groups of individuals, notably in immunosuppressed transplant recipients and fetuses who acquire virus from their mother during pregnancy. In addition, CMV can occasionally cause disease in individuals apart from these groups, such as yourself. While scientists have been highly successful in developing vaccines against many viruses and bacteria that have long plagued humankind (polio, smallpox, measles, diphtheria, pertussis, to name a few), other infectious agents present major challenges, including CMV. Other challenges include developing vaccines for tuberculosis, malaria, and HIV. Despite some of the best minds in the world working on these pathogens, we are not yet at the point where these pathogens can recede into the history books.

The CMV vaccine effort described in the article is work from my lab in which we are trying to develop a completely novel vaccine against CMV by targeting what we believe is an especially vulnerable part of the virus. The work is experimental at this point. While we have made great progress in our animal models, we still need to conduct more experiments in animals before we advance the studies to human clinical trials. While the progress may seem frustratingly slow to you and others who know from first-hand experience the pain and consequences of CMV disease, I want to assure you that we are working as hard and as fast as we can. Our goal is to get it right. The costs and challenges in conducting human clinical trials are enormous, and our goal is to demonstrate in our animal models that we can eliminate as many unknowns before we advance the work to people.

I also want to emphasize that our research is an example of Americans’ taxes and donations at work. My research, and that of almost all researchers in the U.S., is funded through grants awarded by the National Institutes of Health, which is allocated money through the budgetary process of Congressional allocation and the signature of the President. We take this fiduciary responsibility very seriously, and I can speak for the countless other researchers across the country when I assure you that we are absolutely committed to the mission of using these funds in the most cost-effective and efficient manner to advance human health and well-being.

I am not a clinician, and therefore, not in a position to address specific medical issues related to your disease or the potential for CMV activation. As a basic scientist, however, I can tell you that, in general, CMV infection stimulates the immune system to develop long-term immune responses that prevent CMV disease in the future. While this is not necessarily a guarantee for you, there are many clinicians and scientists working diligently so that you and others never have to experience CMV again. I wish you all the very best, and please feel free to ask questions. If I don’t have an answer, I will find someone who does.

Sincerely, Barry”

Barry JD, and Barry PA. Using the nonhuman primate model of HCMV guide virus development. Viruses 6:1481-501, 2014. PMC4014706


Emily S. Rothwell, doctoral student, has received a two-year award from the Bay Area Predoctoral Training Consortium in Affective Science (BARATC) entitled “Affiliative Behavior and the Neurocircuitry of Reward.”

Dennis J. Hartigan-O’Conor, M.D., Ph.D., received a two-year grant from the National Institutes of Health entitled “Neural circuitry of reward and aversion in monkeys.”

Dr. Simon Cherry, Core Scientist, and Alice Tarantal, with collaborator Dr. Julie Suncliffe, presented “Bi-terminally PEGylated Fluorescent Virus-like Particles for Imaging of Tumor Xenograft Mouse and in Nonhuman Primates” at the World Molecular Imaging Congress, September 17-20, 2014, in Seoul, Korea. The findings presented were from the Phase IIb/III Clinical Trial Study Investments in Science and Engineering (RISE) award entitled: “UC Davis Center of Excellence in Translational Molecular Imaging.”


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Out & About

Conferences and Symposia

SNARF research highlights


Dr. Emily S. Rothwell, postdoctoral fellow, presented posters entitled “Socially Monogamous Taiwan Vole (Microtus kikuchii),” “Chronic Intranasal Oxytocin Affects Social Preference Behavior in Voles, Mice, and Monkeys,” and “Activation.”


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**Spotlight on Services**

The UC Davis – CNPRC partnership for growth of the research enterprise represents an unprecedented commitment of resources to a long-term vision of CNPRC-initiated research that addresses the medical challenges that face the world today and that will continue to arise in the future.

UC Davis has been working towards a transformational level of improvement to our physical plant. It is exciting to see the high level of support we are receiving in grounds and landscape beautification around the Center. Trees and shrubs have been manicured, leaves, weeds and grass clipping have been removed, and many of the shrub beds located throughout the CNPRC grounds have been mulched.

Parking services has also been working to provide the Center with a lower cost parking option in a gravel lot to the north of the administration building. We are hoping to have this new parking option available by the first of the new year, and will keep everyone informed on the progress of this project and how to purchase a permit for this area.

Campus facilities crews have and will continue to be working indoors as well on general maintenance and painting projects. We have received a significant commitment from our campus facilities colleagues to invest in the highest priority deferred maintenance projects that we have asked them to address.

Following are a few other examples of UC Davis and CNPRC teamwork and mutual commitment to advancing the research enterprise.

**New Faculty Positions.** The campus has made an exceptional promise of 10 full faculty positions as part of the CNPRC director recruitment. These positions are essential to our long-term growth, and the faculty will be located within five Schools and Colleges (Medicine, Veterinary Medicine, Engineering, Biological Sciences, and Letters and Science).

**Participation of Campus Leadership During the Upcoming NIH Site Visit.** The Chancellor, Provost, Vice Chancellor for Research, and the five Deans (or their representatives for those unavailable) will be on hand on the morning of the site visit to speak briefly to the reviewers about the campus’ commitment to the CNPRC.

**STARS Award.** The UC Davis campus applied for and was awarded a Strategic Teaching Acquisition and Retention (STARS) award from the UC Office of the President as part of the recruitment package for the new director. This $6.6M award is an interest-free loan from the Office of the President that will provide new resources to faculty recruitments in the next several years. This award is a powerful statement of the dedication of the campus and University of California to the long-term mission of the CNPRC.

The enhancements to the CNPRC physical plant and work environments and dedication to our research programs are clear examples of the UC Davis campus administration’s support of the significant impact that our collective efforts have on advancing human and animal health. It is clear that the CNPRC is a valued and integral component of the UC Davis biomedical research mission and each of us can be proud of our individual and collective contributions!

New signage has been produced by campus to demonstrate to our visitors the close collaborative ties to UC Davis. The image chosen is of a sculpture depicting monkeys at a temple in India. The story behind the sculpture has a number of ties with our mission here at the CNPRC – respect, perseverance, strength and service. Look for a plaque in the lobby with the story behind the image. Photo by: Photo Dharma, Flickr

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**Decades of Service to the Scientific Community**

Pathogen Detection celebrates 30th anniversary of publication

Thirty years ago the CNPRC was at the forefront of discovering the role of retroviruses as the causative agent for Acquired Immunodeficiency Syndrome (AIDS). Dr. Murray Gardner, emeritus Professor of Pathology at the UC Davis School of Medicine, often refers to the CNPRC as the “home” of simian AIDS, as early isolates of retroviruses related to human immunodeficiency virus (HIV) were identified in colony animals and studied by researchers here.

In 1982, the late Nicholas Lerche, D.V.M., M.P.V.M., applied his expertise in epidemiology to investigate an unusual outbreak of immune deficiency that was occurring in a population of chimp monkeys housed in outdoor corrals. In a series of elegant studies first published in 1984, Dr. Lerche demonstrated that this immune deficiency disorder was the result of an infectious agent and spread by direct contact. The subsequent discovery and characterization of Simian Retrovirus (SRV) by Dr. Lerche and CNPRC colleagues led to the identification of another retrovirus, Simian Immunodeficiency Virus (SIV). The report of SIV was fortuitous in its timing, occurring almost exactly at the same time as HIV was causing disease of unknown origins around the world. SIV infection in macaque monkeys became the critically important animal model for studying HIV infection in humans, leading to many important discoveries and treatments for HIV/AIDS.

The Pathogen Detection laboratory (PDL) emerged from this early period of retrovirus discovery. In 1985, before there were commercial tests on the market, PDL originated as the AIDS Virus Diagnostic Laboratory, founded to develop and provide one of the only testing facilities for the newly discovered public health threat – HIV. The laboratory began by resurrecting an abandoned research building on the outskirts of campus, sandwiched between the railroad tracks and the catwalk. This new laboratory provided serology and culture results for researchers, blood banks, public health, reference and hospital laboratories, and private physicians across the country.

In 1987 the AIDS Virus Diagnostic Laboratory expanded its services to provide virus testing for nonhuman primates in support of animal models for HIV research. The laboratory played a major role in ensuring CNPRC animals remained healthy by monitoring the eradication of SRV, SIV and Simian T-cell Leukemia Virus (STLV) from the Center’s monkey colonies.

Dr. Michael Lairmore, Dean of the UC Davis School of Veterinary Medicine, was one of the lab’s early collaborators on STLV testing. As diagnostic kits for HIV became commercially available and the need for nonhuman primate testing increased, JoAnn Yee, one of the founding staff members from the AIDS Virus Diagnostic Laboratory, began working with Dr. Lerche in the newly formed Simian Retrovirus Reference Laboratory (SRRL). At its peak, SRRL processed over 10,000 samples from more than 100 clients for up to half a dozen different agents each year. With growth and expansion of testing for other pathogens identified in nonhuman primates, SRRL underwent a name change to Pathogen Detection Laboratory. The Pathogen Detection resource recently became part of a larger effort in immunology and pathogen detection, as a key component of the Immunology and Pathogen Detection Resources Core.

The legacy of Dr. Lerche’s scientific contributions to pathogen detection remains today. Pathogen Detection Resources continues to offer testing, but the focus has expanded to providing training, proficiency testing, troubleshooting, reagents, controls, and protocols. The staff’s extensive experience in resolving problem cases is a key factor in their ability to develop new assays and provide a unique service not available in other laboratories.
We are honored to have Angela Haczku, M.D., Ph.D., joining the CNPRC as an Affiliate Scientist. Dr. Haczku is a Professor of Medicine and Director of the Translational Lung Biology Center at the Pulmonary, Critical Care and Sleep Medicine Division, UC Davis. She was trained in internal and pulmonary medicine at the University of Debrecen, Hungary, and obtained a Ph.D. at the Imperial College, London, UK, completing her post-doctoral training in immunology at the National Jewish Medical and Research Center, Denver, Colorado. She studies the effects of environmental exposures on lung biology, and is internationally recognized as an expert in pulmonary immunology, innate immunity and experimental modeling of lung inflammation. Her group was one of the few that raised the immunoprotective significance of surfactant proteins A and D in allergen and ozone induced airway inflammation and the first one that described a negative feedback regulation between these lung collectins and pro-inflammatory processes. Her team recently established a unique murine model of combined psychosocial stress and asthma and discovered that these conditions synergistically impair glucocorticoid receptor function.

Dr. Haczku has a special interest in the study of lung diseases that co-occur with asthma, particularly idiopathic pulmonary fibrosis, interstitial lung disease, and allergic asthma. Dr. Haczku studies the effects of environmental exposures on lung biology, and is internationally recognized as an expert in pulmonary immunology, innate immunity and experimental modeling of lung inflammation.

Haczku to work with Respiratory Diseases Unit in the new Respiratory Disease Center

The challenge: Pea gravel helps keep rhesus monkeys active and healthy at the California National Primate Research Center. The macaques receive mental stimulation and enrich their diets by foraging in the gravel and grass in their outdoor corrals. And the gravel, unlike the grass, can be easily changed to keep the habitat clean.

But the soiled gravel poses a weighty problem for the campus—70,800 pounds a week, or 1,340 tons a year, that gets trucked to a landfill. Disposing of the old gravel costs more than what the primate center pays to buy it new. But more important to campus sustainability efforts, the gravel created a mountaneous obstacle to reaching UC-wide goals of zero waste by the year 2020. Here’s how they are solving the problem.

Resource savings, improvements to long-term sustainability and efficiency, and enhanced animal care

The opportunity: Of 6,520 tons of annual waste, monkey gravel comprises more than 25 percent. By weight, 1,840 tons of gravel is equal to 129 million empty water bottles.

A True Aggie Collaboration

Finding a solution involved sustainability officials, primate center leaders and campus facilities employees—a number of them alumni:

Sid England, Ph.D. ’95, assistant vice chancellor for environmental stewardship and sustainability
Michelle La ’10, waste reduction and recycling coordinator
Dallas Hyde, Ph.D. ’76, professor and former director of the California National Primate Research Center
Jennifer Short ’82, assistant director of colony management and research services at the primate center

"This was collaboration in the best sense with everyone working toward a common goal," said David Phillips ’88, who oversees the wastewater plant as utilities director.

Sustainability officials worked with the primate center to find solutions that would help keep their habitat clean while helping the campus achieve its sustainability goals. The challenge was to find a way to treat the gravel for use within the primate center, to keep the landfilling and buying new gravel at bay.

"We're not just trying to keep the campus sustainable, we're trying to show leadership in this area," said Jennifer Short, director of Colony Management and Research Services at the primate center.

The primate center and the wastewater treatment plant have worked together since the center opened in 2005 to minimize the amount of non-organic material sent to the landfill. However, the primate center has grown since then, and finding a solution that worked for both the primate center and the wastewater plant was a challenge.

The solution: Recycling gravel will save $40,000 a year compared to the costs of landfilling it and buying replacement gravel.

Dr. Haczku has moved into experimental modeling of lung inflammation. Her group was one of the few that raised the immunoprotective significance of surfactant proteins A and D in allergen and ozone induced airway inflammation and the first one that described a negative feedback regulation between these lung collectins and pro-inflammatory processes. Her team recently established a unique murine model of combined psychosocial stress and asthma and discovered that these conditions synergistically impair glucocorticoid receptor function.

"Dr. Haczku is an outstanding UC Davis basic scientist researcher," said Jennifer Short, director of Colony Management and Research Services at the primate center. "She brings a wealth of knowledge and expertise to our team, and we look forward to working with her."
Understanding Early HIV Infection And identifying potential therapeutic targets

The mucosal lining of the human gastrointestinal tract is on the frontline of immune defenses, crucial in preventing infection and controlling the spread of intestinal pathogens. It must respond rapidly to eradicate pathogens, while simultaneously maintaining tolerance to commensal bacteria. This balance is critical to the maintenance of intestinal homeostasis.

When an individual is first infected with HIV, the virus causes a breach in the mucosal defense and the gut goes through a series of responses that lead to deficiencies in the immune system and defects in the epithelial barrier, which result in chronic inflammation, disease progression, and an increased susceptibility to pathogens. In HIV-infected individuals, systemic immune activation is also increased through a translocation of intestinal microbial products into the systemic circulation.

The biology behind this breakdown in the integrity of the gut barrier has been well studied, but what happens before this cascade of events was not understood until the following research study was conducted at the CNPRC at UC Davis.

Sayta Dandekar, Ph.D., Core Scientist in the CNPRC Infectious Disease Unit, Professor and Chair Medical Microbiology and Immunology, UC Davis School of Medicine, is using the rhesus monkey model of HIV, Simian Immunodeficiency Virus (SIV), to investigate early state dysfunction in the gut mucosal response and to determine the mechanisms contributing to the inability of the host to control these infections. This knowledge will be crucial in identifying therapeutic targets for mucosal protection against the virus and co-infections.

To conduct her research, Dr. Dandekar teamed with veterinarians from CNPRC primate medicine services and investigators from across UC Davis – Departments of Medical Microbiology and Immunology, Molecular and Cellular Biology, Biochemistry and Molecular Medicine, and Food Science and Technology. The research results were published in August 2014 PLoS Pathogens ("Early mucosal sensing of SIV infection by paneth cells induces IL-1β production and initiates gut epithelial disruption ").

A focus of the investigation was Paneth cells, an integral part of the gastrointestinal tract. Paneth cells are one of the principal cell types in the epithelial lining of the small intestine and play a crucial role in epithelial cell renewal, immunity and host-defense, and produce antimicrobial substances that have been shown to have a significant effect on bacteria. While the mechanism by which Paneth cells sense and respond to virus infections, and to clarify the importance of the gut epithelium in HIV infection. Understanding is sought for the gut epithelium not as just a target of disease but also as initiator of immune responses to viral infection, which can be strongly influenced by commensal bacteria.

Another focus of the study, investigated for the first time, the immune response by the gut mucosa to commensal bacteria (such as Lactobacillus plantarum) in the context of early HIV infection. The researchers found that the host maintains its ability to distinguish pathogenic (Salmonella typhimurium) and commensal bacteria and mount the proper immune response.

The research findings also suggest a supportive role of commensal bacterium L. plantarum in overcoming SIV-induced gut inflammation and epithelial disruption, raising the possibility of using L. plantarum to intervene the early mucosal-viral interactions that may influence gut immunological effects. In addition to its anti-inflammatory effects, they observed enhanced recruitment of T helper 17 cells (which can give rise to protective cells) in response to L. plantarum, suggesting a supportive role of L. plantarum in overcoming SIV-induced gut inflammation and epithelial tight junction disruption. This recruitment of T helper 17 cells may have a role in epithelial repair.

“What is potentially exciting about this research is the demonstration that the early stages of gut inflammation and damage can be intervened by the targeted probiotic bacteria” states Dr. Dandekar.

However, the findings also discovered unintended consequences that an L. plantarum probiotic therapeutic adjutant may include the establishment of silent viral reservoirs. The results raise an important consideration in the development of probiotic therapies for HIV infection, and highlight the need for better characterization of probiotic bacterial functions and effects.

By understanding the mechanisms that underlie the host / microbeota relationship in health and HIV disease, it will be possible to capitalize on their evolved synergy while identifying gaps in mucosal defenses that can be fortified through therapy.

This study highlights the need for future investigations to determine the mechanisms of Paneth cell sensing and response to virus infections, and to clarify the importance of the gut epithelium in HIV infection. Understanding is sought for the gut epithelium not as just a target of disease but also as initiator of immune responses to viral infection, which can be strongly influenced by commensal bacteria.