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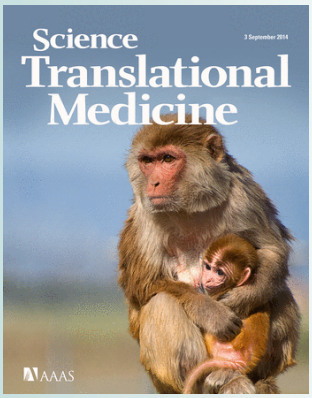

Contents

Source of Milk Determines Strength of Immunity

Team effort between the CNPRC and UCSF

In a study published in *Science Translational Medicine* on September 3, 2014, researchers from the California National Primate Research Center (CNPRC) and the School of Medicine at UC Davis and 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 were surprised at the extent to which these bacteria were found to shape immunologic development. Breast-fed macaques had more "memory" T cells and T helper 17 (T_H17) cells, which are known to fight *Salmonella* and other pathogens.

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."

"What's most startling is the durability of these differences. Infant microbes could leave a long-lasting imprint on immune function." Dennis Hartigan-O'Connor

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 T_H17 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 T_H17 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 Koen 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, as was to be expected in animals receiving different diets.

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.

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From the Director

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 absolutely 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 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 is for us to be the best stewards of our nonhuman primate resource to improve both animal and human health. Whereas those who have served in the military have sometimes had to risk all 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: using 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.

Peter Barry, 11-12-2014

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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 more able to secrete immune defense chemicals called "cytokines", including T_H17 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.

"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," Amir Ardeshir

Further investigation suggested possible components that may drive key differences between the two groups, including arachidonic acid, which stimulates the production of T_H17 cells and is found in macaque breast milk. This chemical was tightly linked to T_H17 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, T_H17 cells, and bacterial genera such as *Prevotella* and *Campylobacter*.

While this research provides a fascinating window into immune cell development in macaques, Hartigan-O'Connor cautions 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 is a developmental shape to the immune system that we don't often consider," Hartigan-O'Connor 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 those 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.

This research was supported by grants from the National Institute of Allergy and Infectious Diseases (K23AI081540), the Bill and Melinda Gates Foundation under a Grand Challenges Exploration award (#52094) and by Office of the Director, NPRC Base Grant (P51-OD011107).

Ardeshir A, Narayan NR, Méndez-Lagares G, Lu D, Rauch M, Huang Y, Van Rompay KK, Lynch SV, and Hartigan-O'Connor DJ. Breast-fed and bottle-fed infant rhesus macaques develop distinct gut microbiotas and immune systems. Sci Transl Med. 6(252):252, 2014. PMC Journal-in-Progress.

New Affiliate Scientists Partner With CNPRC

CNPRC Teams with Schools of Veterinary Medicine and Medicine in Faculty Recruitment

Director 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.

Veterinary Ophthalmologist
Sara Thomasy, D.V.M., PhD, DACVO

"The partnering of the CNPRC with the Vision Science program is part of a broader strategic goal of the UC Davis campus to be the preeminent research center of excellence in vision science" said Director Barry.

Developing new strategies to treat blinding eye diseases

Anna 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.

Anna La Torre, Ph.D.

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 maculae 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 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 is Associate Editor of Allergy as well as Respiratory Research and editorial board member of the Journal of Allergy and Clinical Immunology, American Journal of Respiratory, Cell and Molecular Biology and American Journal of Physiology.

Angela Haczku, M.D., Ph.D.

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/AII 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 immunology, 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.

Respiratory Disease Center, CNPRC, UC Davis

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 in 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 rhesus 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 numerous discoveries and treatments for HIV/AIDS.

Dr. Nick Lerche was the Director of PDL until his retirement in 2012.

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 it's 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.

SIV infection in macaque monkeys became the critically important animal model for studying HIV infection in humans, leading to numerous discoveries and treatments for AIDS.

Low speed centrifuge for general lab use such as separating blood cells from plasma. Photo circa ~1984.

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, trouble shooting, 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.

Out & About

Conferences and Symposia

Sharing CNPRC research highlights

Representing the Brain, Mind, and Behavior Unit: Dr. Karen L. Bales, Core Scientist and Unit Leader, gave invited talks at the following meetings: the International Behavioral Neuroscience Society in Las Vegas, Nevada, June 10–15, 2014, entitled: *"Chronic Intranasal Oxytocin: Long-term Effects of a Reproductive Hormone on Behavior and Neural Systems"*; the Schizophrenia International Research Society, April 5–9, 2014, in Florence, Italy, entitled *"Translational Paradigms for Social Cognition in Rodents and Nonhuman Primates"*; and at the Collaborative Biomedical Research Conference on the Vole Animal Model, July 25–26, 2014, in Portland, Oregon, Oregon Health and Science University, entitled *"Sex Differences in Effects of Chronic Intranasal Oxytocin: Voles, Mice, and Monkeys"*.

Dr. Tamara Weinstein, Assistant Project Scientist, gave an oral presentation at the International Behavioral Neuroscience Society in Las Vegas, Nevada, June 10–15, 2014, entitled *"Neural Correlates of Social Interaction 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 Distribution of Oxytocin and Vasopressin 1a Receptors in the Socially Monogamous Taiwan Vole (Microtus kikuchii)"*; and at the International Meeting for Autism Research, May 15–17, Atlanta, Georgia, entitled *"Distribution of Oxytocin Receptors and Vasopressin 1a Receptors in the Titi Monkey: an Emerging Animal Model for the Study of Social Attachment"*.

Dr. Brenda McCowan, Core Scientist, was an invited speaker at Universiti Putra Malaysia, Kuala Lumpur, Malaysia, on May 30, 2014. Her talk was entitled: *"Planet of the Monkeys: Animal Welfare at the Human-Macaque Interface in South, East, Southeast Asia and Beyond"*.

At the 25th Congress of the International Primatological Society. Hanoi, Vietnam, August 11–16, 2014, **Dr. Brianne Beisner**, postdoctoral fellow, presented a talk entitled *"Receipt of Silent-Bared-Teeth Signals in Peaceful Contexts Predicts Conflict Policing Behavior in Captive Rhesus Macaques"*, and posters entitled: *"Human–Macaque Interactions Influence Social Behavior in Commensal Rhesus Macaques in Northern India"* and *"Factors Influencing Human-Macaque Aggression in Commensal Rhesus Macaques in Northern India"*. **Dr. J. Jin** presented posters entitled *"Social Separation Affects Personality and Affiliative Behaviors in Captive Rhesus Macaques (Macaca mulatta)"* and *"Personality Affects Changes in Friendships After Social Separation in Rhesus Macaques (Macaca mulatta)"*.

Dr. John Capitanio, Core Scientist, gave an invited symposium at the 25th Congress of the International Primatological Society. Hanoi, Vietnam, August 11–16, 2014, entitled: *"Mechanisms of the Social Relationship-health Link"*. He also presented a talk at the 4th Purdue Symposium on Psychological Sciences, West Lafayette, Indiana, May, 2014 entitled *"Perspectives on Personality in Nonhuman Primates"*.

Rebecca H. Larke, graduate student, presented a poster at the International Meeting for Autism Research, May 15–17, Atlanta, Georgia, entitled *"Serotonin 1a Agonism Selectively Inhibits Affiliation in the Titi Monkey: Relevance to Social Deficits and Hyperserotonemia in Autism"*; and at the Collaborative Biomedical Research Conference on the Vole Animal Model, July 25–26, 2014 in Portland, Oregon, Oregon Health and Science University, entitled *"Fluoxetine Exposure During Development Alters Later Social Behavior in the Prairie Vole (Microtus ochrogaster)"*. Also at this conference, **Elizabeth Sahagun**, staff, presented a poster entitled *"Continuing Oxytocin Treatment into Adulthood Does Not Ameliorate Pair-bond Deficits Found in Male Prairie Voles"*.

Dr. Melissa Bauman gave an oral presentation at the International Behavioral Neuroscience Society 'Current Advances in Animal Models of Neurodevelopmental Disorders', June 2014, in Las Vegas Nevada entitled *"A Nonhuman Primate Model of Maternal Immune Activation"*.

Dr. Erin Kinnally gave a talk at the American Association for the Advancement of Science in Chicago, Illinois, February 14–15, 2014 entitled *"Early Life Stress and Epigenetic Plasticity in Rhesus Macaques"*; and at the ZIF Conference on Adaptive Behavioral Development University of Bielefeld, Germany September 29–October 1, 2014 entitled *"Social Mechanisms in the Transgenerational Effects of Paternal Early Stress"*.

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. John Capitanio,** Core Scientist, gave an invited talk for the symposium on 'Different insights about social processes in primates' entitled *"Lonely monkeys: When Social Desire and Social Attainment Clash";*
- **Dr. Brenda McCowan**, gave an oral presentation entitled *"Connections Matter: Influence of Social Networks and Their Perturbations on Key Indicators of Health in Rhesus Macaque Societies";*
- **Dr. Tamara Weinstein**, Assistant Project Scientist, gave a poster presentation entitled *"The Effects of Chronic Intranasal Oxytocin on Response to Novelty in Juvenile Titi Monkeys (Callicebus cupreus)";*
- **Dr. Sara M. Freeman**, postdoctoral fellow, gave an oral presentation entitled *"Effect of Reward Type on Reinforced Learning Behavior in Laboratory-housed Coppery Titi Monkeys (Callicebus cupreus)";*
- **Dr. Jessica Vandeleest**, postdoctoral fellow, presented two posters entitled *"Personality is Related to Immune Activity in Rhesus Monkeys (Macaca mulatta)"* and *"Sociability is Related to Lower Baseline Immune Activity in Rhesus Monkeys (Macaca mulatta)";*
- **Dr. Brianne Beisner,** postdoctoral fellow, presented a poster entitled *"Experimental Removal of High-ranking Natal Males Alters the Structure of Silent-bared-teeth Display Networks in Captive Groups of Rhesus Macaques (Macaca mulatta)"*. Dr. Beisner also presented a talk entitled *"Mean Dominance Relationship Certainty is Better Than Rank at Predicting Diarrhea Incidence and Wounding in Captive Rhesus Macaques (Macaca mulatta)";*
- **Dr. Darcy Hannibal**, research scientist, gave an invited podium presentation entitled *"Matriline Fragmentation and Alopecia in Captive Outdoor Socially-housed Rhesus Macaques (Macaca mulatta)"* at the ASP meeting session 'Symposium on Chronic Hormones and Demographic Variables: Center-Wide Studies on Non-Human Primate Well-Being';
- **Rocio Arias Del Razo**, graduate student, presented a poster entitled *"Chronic Intranasal Oxytocin Affects Social Preference Behavior in Juvenile Titi Monkeys (Callicebus cupreus)";*
- **Emily S. Rothwell**, graduate student, presented a poster entitled *"Validation of a Partner Preference Test in Coppery Titi Monkeys (Callicebus cupreus)";*

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• **Dr. Allison Heagerty**, postdoctoral fellow, gave a talk entitled *"Rhesus Macaque Females Allocate Grooming Differently in the Wild and Captivity";*
• **N.G. Sharp**, graduate student, gave two oral presentations entitled *"The Influence of Personality Composition on Group Dynamics in Sanctuary Chimpanzees (Pan troglodytes)"* and *"The Influence of Key Personalities on Group Dynamics in Captive Chimpanzees (Pan troglodytes)";*
Dr. Benjamin Ragen, previous graduate student, presented a poster entitled *"Mu and Kappa Opioid Receptor Binding in the Forebrain of the Monogamous Titi Monkey (Callicebus cupreus)";*
• **M.T. Bennett,** undergraduate student, presented a poster entitled *"Effect of 5HTTLPR Genotype and Social Dominance Rank on Infant Cortisol in Corral-living Rhesus Macaques."*
• **K. Baker** gave a talk entitled *"Pairing Rhesus Macaques (Macaca mulatta): Methodology and Outcomes at Four National Primate Research Centers";*
• **Sarah Carp**, previous staff member, presented a poster entitled *"Validation of a Partner Preference Test in Coppery Titi Monkeys (Callicebus cupreus)";*
• **K.R. Davidek**, staff member, presented a poster *"Affiliative Relationships, Alliance Support, and Personality Influence Cumulative Receipt of Subordination Signals in Rhesus Macaque Societies";*
• **K.R. Finn**, staff, presented a poster entitled *"Affiliative Use of the Bared Teeth Display in Outdoor Captive Rhesus Macaques";*
• **K.R. Glass**, undergraduate student, presented a poster entitled *"5HTTLPR Gene, Mother's Social Dominance, and Infant Cortisol in Rhesus Macaques (Macaca mulatta) Living in Large Outdoor Enclosures".*

Representing the Infectious Diseases (ID) Unit: Dr. Paul Luciw, ID Unit Leader, attended the Collaboratory of AIDS Researchers for Eradication conference in Chapel Hill, North Carolina, June 11–13, 2014. His poster was entitled *"RT-SHIV/Macaque Model for Studies of Viral Reservoirs and Induction Activation Therapy".*

Dr. Jay V. Solnick, Core Scientist, gave invited talks at the following venues: The 11th International Workshop on Pathogenesis and Host Response in Helicobacter Infections, Helsingor, Denmark, July 2-5, 2014, entitled *"Tuning the Host Response: Modulation of H. pylori Virulence During Acute Infection"*; The University of Sassari, Sassari, Italy, June 30, 2014 entitled *"Helicobacter pylori: Pathogen, Symbiont, or Both?"*; Department of Microbiology and Immunology at the University of Michigan, Ann Arbor Michigan, April 3, 2014, entitled *"Functional Plasticity in the Helicobacter pylori Type IV Secretion System"*; and the Center for Inflammation and Mucosal Immunology, University of Florida, January 23, 2014, entitled *"Tuning the Host Response: Functional Plasticity in the H. pylori Type IV Secretion System".*

Representing the Reproductive Sciences and Regenerative Medicine (RSRM) Unit: Dr. Alice Tarantal, RSRM Unit Leader, and collaborator Gerald Lipshutz presented at the 17th Annual Meeting of the American Society of Gene and Cell Therapy, May 21-24, Washington, DC, *"Gene Transfer in Infant Nonhuman Primates can Induce Operational Immunologic Tolerance to Neoantigens".*

Drs. Cynthia Batchelder, Chang Lee, CNPRC research scientists, and Alice Tarantal, presented new findings entitled: *"Natural Scaffolds for In vitro Studies of Kidney Development, Disease, and Tissue Engineering"* at the 12th Annual Meeting of the International Society for Stem Cell Research, June 18-21, Vancouver, Canada.

Dr. Tarantal attended the NHLBI Gene Therapy Research Program Steering Committee meetings on April 30, 2014 and September 15, 2014 at the NIH, Washington, DC.

Drs. **Simon Cherry,** Core Scientist, and Alice Tarantal, with collaborator Dr. Julie Sutcliffe, presented *"Bi-terminally PEGylated Fluorine 18-peptide for Integrin αvβ6-targeting: In vivo Evaluation in Tumor Xenograft Mice and in Nonhuman Primates"* at the World Molecular Imaging Congress, September 17-20, 2014, in Seoul, Korea. The findings presented were from the campus-supported Research Investments in Science and Engineering (RISE) award entitled: "UC Davis Center of Excellence in Translational Molecular Imaging".

Dr. Simon Cherry gave the following invited talks and presentations: **February 2014**: Molecular Imaging and Therapy Seminar, Memorial Sloan Kettering Cancer Center, *"Of Mice and Men: Delivering Molecular Imaging Technology to Advance Biomedical Research";* Keynote Presentation, SPIE Medical Imaging Conference, San Diego, California *"Advancing Technologies for Preclinical Molecular Imaging";* and Shenzhen Institute of Advanced Technology, Shenzhen, China, *"Delivering Molecular Imaging Technology to Advance Biomedical Research".* **April 2014**: BMES Chapter Imaging Conference, Faculty Advisor and Opening Presentation, Davis, California, *"From Mouse to Man: Advances in Imaging Made Clinically Relevant".* **May 2014**: Keynote for the Opening of a microPET Facility, School of Medicine, UNAM, Mexico City, Mexico, *"Preclinical and Basic Research using microPET";* and Symposium on Advances in Molecular Imaging, CLEO 2014, San Jose, California, *"In vivo Molecular Imaging using Cerenkov Luminescence".* **June 2014**: BIO International Convention, San Diego, California, *"Seeing is Believing – How Imaging can Add Value to Early-Stage Assets and Reduce Late-Stage Attrition";* and Gordon Research Conference, Lasers in Medicine and Biology, Holderness, New Hampshire, *"Exploiting the Interface between Nuclear and Optical Radiation for In vivo Biomedical Imaging".* **September 2014**: Mediterranean Thematic Workshops in Advanced Molecular Imaging, Alghero, Sardinia, Italy, *"PET Technology Across Different Scales: Designs Driven by Applications";* and NCI Multi-Scale Imaging in Cancer Biology Workshop, Houston, Texas, *"Translational Cancer Imaging with Positron Emission Tomography".*

Representing Primate Medicine: Dr. Christina Cruzen, Senior Veterinarian, gave oral presentations at the 2014 WNPRC Lab Animal Medicine and Pathology Seminar in Madison, Wisconsin, April 3-4, 2014, entitled, *"Multi-animal Approach to Must-know Diseases", "Primate Taxonomy and Species Identification", and "NHP Management and Applied Regulations"*;

Primate Medicine was well represented at the Association of Primate Veterinarians in San Antonio, Texas, October 15-18, 2014:
• Dr. Christina Cruzen gave a talk entitled, *"Monkeys 101 – Diarrhea Management in Captive NHPs"*

• **Dr. Kari Christe**, Senior Manager of Primate Medicine, gave an oral presentation entitled, *"Refining Water Regulation: Clinical Cases"*

• **Dr. Laura Garzel**, Senior Veterinarian, presented a poster entitled *"Solitary Plasmacytoma of Bone in a Rhesus Macaque (Macaca mulatta)"*

• **Dr. Gregory W. Salyards**, Laboratory Animal/Primate Medicine Resident, gave an oral presentation entitled, *"Pharmacokinetics of Ceftiofur Crystalline Free Acid (CCFA) in Male Rhesus Macaques (Macaca mulatta) after Subcutaneous Administration"* and also presented this title at the American Association of Laboratory Animal Science in San Antonio, Texas, October 19-23, 2014.

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Awards & Honors

UC Davis Honors

'Most accomplished investigator'

Dr. **Alice Tarantal**, Reproductive Sciences and Regenerative Medicine Unit 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 nomination for Dr. Tarantal 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.

'Surprised and Honored'

First recipient of special award

Photo: K. West

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, 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 inagural 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.

Students, Staff and Faculty Earn Accolades

• After years of preparation and a grueling exam, **Dr. Marie Josee Lemoy**, 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 Presynaptic Striatal 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 Dukes 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 provides the essential background against which disease-related brain changes can be understood. http://www.apa.org/science/about/psa/2014/05/distinguished-scientific-awards.aspx

Primate Models in Research

CBRA News Blast: April 22, 2014

In this review article, scientists discuss the importance of primate models for advancing knowledge in biomedical and biological research. Presenting an honest, forthright discussion of the ethical considerations of using nonhuman primates (NHP) in research, and demonstrating the vital role NHP have played in many of the medical and scientific advances of the past century, 14 scientists, including CNPRC researchers Drs. Karen Bales, John Capitanio, and Lisa Miller, collaborated to publish a comprehensive article in the American J. of Primatology entitled "Why Primate Models Matter" on April 15, 2014 (Early View).

'The Neurobiology of Love'

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

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!

The Job Market

The hunt for academic positions

Excerpt from: Science, AAAS, "The Job Market: The Lisa Feldman Barrett lab"; By John Bohannon, September 30, 2014
http://sciencecareers.sciencemag.org/career_magazine/previous_issues/articles/2014_09_30/caredit.a1400245

"One thing is mandatory on a CV for landing a tenure-track job at a top research university, Lisa Feldman Barrett says. "You have to be an author on a paper in a journal like Science, Nature, or PNAS." Even a paper in a prestigious journal is no longer a guarantee of a job. Barrett's coauthor on that 2011 Science paper, Eliza Bliss-Moreau, is in her 6th year as a postdoc at the University of California, Davis.

In many ways, Bliss-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 tease 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 work relies on imaging of monkeys' brains.

Some call it interdisciplinary research, "but our buzzword for this is integrative science," says Alan Kraut, executive director of the APS. He calls Barrett "the poster child" for this cross-cutting approach to research. Bliss-Moreau has followed a similar path.

For her part, Bliss-Moreau is taking the job market struggle in stride, for now. "I love the work that I do. I love being able to teach and mentor in the laboratory." Her aim is "to parlay all of my education and training into an academic job. … We'll see if that happens this year."

Monkeys, Milk and Comedians

October 22, 2014; https://soundcloud.com/youre-the-expert/s2ep14-live-at-the-eugene-mirman-comedy-festival

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

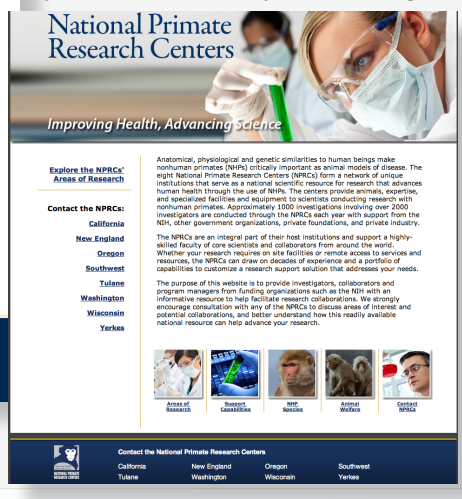
Monkeys, Milk and the NY Times

November 6, 2014; In a Mother's Milk, Nutrients, and a Message, Too by Carl Zimmer, http://www.nytimes.com/pages/science

Drs. Katie Hinde, John Capitanio, Sally Mendoza, and Laura del Rosso collaborated on a study that was covered by the front page of the NY Times Science section, online November 6 and in hard copy on November 7, 2014. Congratulations for the fantastic coverage of great science at the CNPRC!

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

Two dynamic new websites were recently released to provide expanded outreach and research collaborations. The CNPRC's newly designed website went live 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 NPRC). "Friend" us 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 investigators conduct their studies, and to identify collaborative scientists at the NPRCs who can provide guidance on the use of nonhuman primate models and assays.

Research Highlights

Brain, Mind, and Behavior Unit

Loneliness and health

Monkeys, too, can be lonely, even when surrounded by others in a social group

What is loneliness? Is it wishing to be social but not having friends in your social group? More than just a socio-emotional condition, it can be a significant cause of poor health, and is of special concern in the elderly.

Social isolation, or loneliness, has been shown to impact brain and behavior and is recognized as a major risk factor for morbidity and mortality in humans for more than a quarter century.

Many are familiar with the proven health benefits of having long-term social relationships with friends and family. Researchers at the CNPRC and elsewhere have demonstrated the scientific basis for these benefits, showing some physiological reasons for improved health and disease resistance.

However, not all people, nor animals, have the same level of desire to be social. Some prefer to be alone rather than engage with others. 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, 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 animal model to understand the behavioral and biological consequences of loneliness.

"Importantly, our study describes a naturally occurring model of loneliness. Animal models of loneliness are usually induced models – for example an animal is physically separated from its companions. Our research suggests loneliness in monkeys can occur even in the presence of others – just like in humans" emphasizes Dr. Capitanio.

The research was published October 29, 2014 in the online journal PLoS ONE *"A Behavioral Taxonomy of Loneliness in Humans and Rhesus Monkeys (Macaca mulatta)"* and was co-authored with Drs. Louise Hawkley and John Cacioppo 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 that 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 (presumably 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 underlie known variability in adult male rhesus macaques' tendency to affiliate, or "hang out" with others.

The research animals in this study live outdoors in large, half-acre field corrals, in a rich social environment consisting of 80–150 animals. Highly social monkeys show high levels of both simple social behaviors, like approaches, as well as more complex social behaviors, like grooming and contact. At the other end of the spectrum, however, the researchers identified two groups of animals. One group showed low levels of both simple and complex interaction; these animals seem to be relatively uninterested in social interaction, and may be similar to introverted humans. The other group, however, showed levels of simple social interaction that were comparable to those of high-sociable monkeys; however, their levels of complex social interaction were low. These animals appeared unable to convert their strong social interest into desirable social interaction -- much like lonely humans.

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.

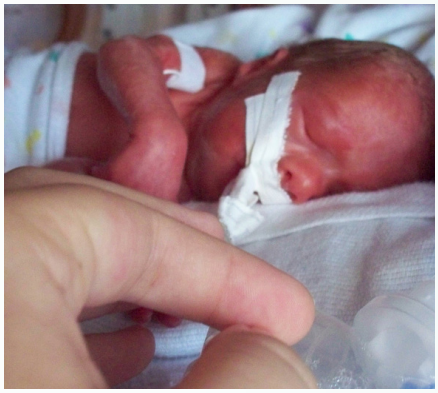
More about Dr. Capitanio's research and publications can be found at www.cnprc.ucdavis.edu/john-p-capitanio/

Respiratory Diseases

Understanding the fetal inflammatory response

Many Affiliate 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 Cincinnati Children's Hospital Medical Center. Dr. Alan H. Jobe, M.D., Ph.D., is a Professor in the Department of Pediatrics at the University of Cincinnati and Director for the Division of Perinatal Biology. Dr. Jobe's research interests include lung maturation and lung injury in the fetus and newborn, the use of antenatal corticosteroids, and lung injury with ventilation of the preterm infant. Suhas Kallapur, M.D., is also a Professor in the Department of Pediatrics at the University of Cincinnati and Director of Neonatology Continuing Medical Education. The Kallapur laboratory is focused on understanding the pathogenesis and mechanisms of fetal inflammatory responses during chorioamnionitis (inflammation of the fetal membranes). Virtually nothing is known about the immune responses of the preterm fetus.

Along with Affiliate Scientist Claire Choughnet, Ph.D. from Cincinnati Children's Hospital Medical Center, Drs. Kallapur and Jobe collaborated with 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 to define the effects of chorioamnionitis on the fetal immune system. Very low birth weight preterm newborns 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 chorion and amnion prior to spreading to 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 Affiliate 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-1/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 the devastating inflammatory disorders often seen in these preterm babies. Findings from this study also suggest that boosting Treg cells, which modulate the immune system, and/or modulating IL-17 may help control the pathogenesis of chorioamnionitis. Overall, this study clearly demonstrated that the fetal rhesus macaque is an excellent model to study mechanisms of inflammation during human fetal development.

Kallapur SG, Presicce P, Senthamaraikannan P, Alvarez M, Tarantal AF, Miller, LA Jobe AH, and Chougnet CA. Intra-amniotic IL-1β induces fetal inflammation in rhesus monkeys and alters the regulatory T cell/IL-17 balance. J Immunol. 2013; 191(3): 1102–1109. PMCID 3720768

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** and **Dr**. **Carolyn Black,** postdoctoral fellows. Burke and 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 Genes 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" (*Burke*)*.

Dr. Kent Pinkerton, Core Scientist, traveled worldwide to share his research on climate change: *"Global Issues in Science and Health"* Global Science Forum and Workshop, Kyoto Sangyo University, March 6, 2014, Kyoto, Japan; *"The Safety of Nanomaterials from a Human Exposure Perspective"*, 24th Annual International Conference on Soil, Water, Energy, and Air, Association for Environmental Health and Sciences Foundation, March 19, San Diego, California; 'Climate Change and Health: Knowledge Gaps and Research Needs', *"Going to Extremes: The Impact of Climate Change on Occupational and Environmental Health"*, May 9, 2014 Oakland, California; 'Climate Change and Global Health, *"Health Impacts of Climate Change"*, 32nd Annual Occupational and Environmental Medicine Symposium May 10, Sacramento, California; 2014 *"How to Study the Aging Lung"*, Postgraduate Course, International Conference of the American Thoracic Society, May 17, San Diego, California; and *"Women and Lung Disease: Gender Differences and Global Health Disparities"*, Co-Chair, International Conference of the American Thoracic Society, May 20, 2014, San Diego, California.

Dr. Miller also gave a seminar entitled *"The Intersection of Environment and Immunity During Infancy: 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 Infancy: 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 Regenerative Medicine

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

Core Scientists in the Reproductive Sciences and Regenerative Medicine Unit contribute to the CNPRC mission through a range of collaborative opportunities and services to the greater research community, and by mentoring trainees at all levels (undergraduates to fellows to junior faculty). The programs in the Unit are highly integrated with the UC Davis Clinical and Translational Science Center (CTSC), Stem Cell Program, Institute for Regenerative Cures, Center for Molecular and Genomic Imaging, West Coast Metabolomics Center, and the Radiochemistry Research and Training Facility. One primary example of unique 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 Transfer for Heart, Lung, and Blood Diseases, directed by Unit Leader, Dr. Alice Tarantal.

Established in 2001, this program is unique to the CNPRC and serves a crucial role in the research community by addressing essential questions in gene delivery and providing 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 U.S. in research institutions such as: Beckman Research Institute at the City of Hope, Childrens 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 at St. Louis, to name a few. The established infrastructure and expertise in the program can rapidly design and test new paradigms, move 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-severe 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, acid 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 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 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 thus overcoming regulatory barriers. The leap from preclinical discovery to human subjects research is 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, tissue 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.ucdavis.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 will continue to address bottlenecks to improving human health and healthy aging.

Smith BK, Collins SW, Conlon TJ, Mah CS, Lawson LA, Martin AD, Fuller DD, Cleaver BD, Clément N, Phillips D, Islam S, Dobjia N, and 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. Hum Gene Ther 24:630-640, 2013. PMCID: PMC3689178

Infectious Diseases Unit

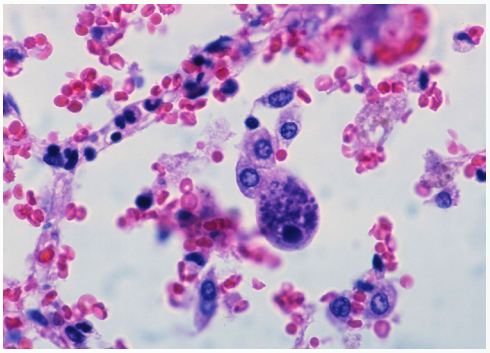
Connecting with the Community

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 research 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.



"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

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,
Peter Barry"

Eberhardt MK, Deshpande A, Chang WL, Barthold SW, Walter MR, and Barry PA. Vaccination against a virus-encoded cytokine significantly restricts viral challenge. J Virol. Nov 2013; 87(21): 11323–11331. PMCID: PMC3807330

Publications

January 2014 – October 2014

Ardeshir A, Narayan NR, Méndez-Lagares G, Lu D, Rauch M, Huang Y, Van Rompay KK, Lynch SV, and Hartigan-O'Connor DJ. Breast-fed and bottle-fed infant rhesus macaques develop distinct gut microbiotas and immune systems. Sci Transl Med. 6(252):252, 2014. PMC Journal-in-Progress

Assaf BT, Mansfield KG, Strelow L, Westmoreland SV, Barry PA, and Kaur A. Limited dissemination and shedding of the UL128 complex-intact, UL/b'-defective rhesus cytomegalovirus strain 180.92. J Virol. 88(16):9310-9320, Epub 2014 Jun 4. PMID: 24899204. PMC Journal-in-Progress

Batchelder CA, Duru N, Lee CCI, Baker CAR, Swainson L, McCune JM, and Tarantal AF. Myeloid-lymphoid ontogeny in the rhesus monkey (*Macaca mulatta*). Anat Rec (Hoboken) 297:1392-1406, 2014. PMCID: PMC4120262

Carbonaro Sarracino DA, Tarantal AF, Lee CCI, Martinez M, Jin X, Hardee C, Geiger S, and Kohn DB. Effects of vector backbone and pseudotype on lentiviral vector-mediated gene transfer: Studies in infant ADA-deficient mice and rhesus monkeys. Mol Ther 22:1803-1816, 2014. PMC Journal-in-Progress

Chaffin CL, Latham KE, Mtango NR, Midic U, and VandeVoort CA. Dietary sugar in healthy female primates perturbs oocyte maturation and *in vitro* preimplantation embryo development. Endocrinology 155:2688-2695, 2014. PMCID: PMC4060180

Chapalamadugu KC, VandeVoort CA, Settles ML, Robison BD, and Murdoch GK. Maternal bisphenol A exposure impacts the fetal heart transcriptome. PLoS ONE 9:e89096, 2014. PMCID: PMC3934879

Deere JD, and Barry PA. Using the nonhuman primate model of HCMV to guide vaccine development. Viruses 6(4):1483-501, 2014. PMCID: PMC4014706

Deere JD, Kauffman RC, Cannavo E, Higgins J, Villalobos A, Adamson L, Schinazi RF, Luciw PA, and North TW. Analysis of multiply spliced transcripts in lymphoid tissue reservoirs of rhesus macaques infected with RT-SHIV during HAART. PLoS One. 2014 Feb 5;9(2):e87914. doi: 10.1371/journal.pone.0087914. eCollection 2014. PMCID:PMC3914874

Fourati S, Vaccari M, Gordon SN, Schifanella L, Cameron M, Keele BF, Shen X, Tomoras GD, Billings E, Rao M, Chung AW, Dowell K, Bailey-Kellogg C, Brown E, Ackerman ME, Liyanage NP, Vargas-Inchaistegui DA, Whitney S, Doster MN, Binello N, Pegu P, Montefiori DC, Foulds K, Quinn DS, Donaldson M, Liang F, Loré K, Roederer M, Koup RA, McDermott A, Ma ZM, Miller CJ, Phan TB, Forthal DN, Blackburn M, Caccuri F, Ferrari G, Thompson D, Robert-Guroff M, Ratto-Kim S, Kim JH, Michael NL, Phogat S, Barnett SW, Tartaglia J, Venzon D, Stablein DM, Alter G, Sekaly RP, and Franchini G. Modulation of RAS Pathways as a Biomarker of Protection against HIV and as a Means to Improve Vaccine Efficacy. AIDS Res Hum Retroviruses. 2014 Oct;30 Suppl 1:A99. doi: 10.1089/aid.2014.5182b. PMID: 25357995. PMC Journal-in-Progress

Freeman S, Walum H, Inoue K, Smith A, Goodman M, Bales K, and Young L. Neuroanatomical distribution of oxytocin and vasopressin 1a receptors in the socially monogamous coppery titi monkey (*Callicebus cupreus*). Neurosci 10.1016/j.neuroscience, 2014. PMCID: PMC4083847

Freeman S, Inoue K, Smith A, Goodman M, and Young L. The neuroanatomical distribution of oxytocin receptor binding and mRNA in the male rhesus macaque (*Macaca mulatta*). Psychoneuroendocrinology 45, 128–141, 2014 PMCID: PMC4043226

Gaulke CA, Porter M, Han YH, Sankaran-Walters S, Grishina I, George MD, Dang AT, Ding SW, Jiang G, Korf I, and Dandekar S. Intestinal epithelial barrier disruption through altered mucosal microRNA expression in human immunodeficiency virus and simian immunodeficiency virus infections. J Virol 88:6268-6280, 2014. PMC Journal-in-progress

George MD, Hu W, Billingsley JM, Reeves RK, Sankaran-Walters S, Johnson RP, Dandekar S. Transcriptional profiling of peripheral CD8+T cell responses to SIVΔnef and SIVmac251 challenge reveals a link between protective immunity and induction of systemic immunoregulatory mechanisms. Virology. 2014 Oct 1;468-470C:581-591. doi: 10.1016/j.virol.2014.09.013. [Epub ahead of print] PMID: 25282469. PMC Journal-in-progress

Gupta S, Pegu P, Venzon DJ, Gach JS, Ma ZM, Landucci G, Miller CJ, Franchini G, Forthal DN. Enhanced *in vitro* transcytosis of simian immunodeficiency virus mediated by vaccine-induced antibody predicts transmitted/founder strain number after rectal challenge. J Infect Dis. 2014 May 21. pii: jiu300. [Epub ahead of print] PMID: 24850790. PMC Journal-in-progress

Hara Y, Yuk F, Puri R, Janssen WG, Rapp PR, and Morrison JH. Presynaptic mitochondrial morphology in monkey prefrontal cortex correlates with working memory and is improved with estrogen treatment. Proc Natl Acad Sci U S A 111:486-491, 2014. PMCID: PMC3890848

Publications, cont'd pg 15

Grants

Peter Barry, Ph.D., with co-investigator **Alice Tarantal**, Ph.D., (for Louis Picker at OHSU) received a Gates Foundation award titled "*Development of Attenuated CMV Vectors for an HIV/AIDS Vaccine"*

Peter Belafsky, M.D., Ph.D., and co-PI **Alice Tarantal**, Ph.D., received a two-year grant from the California Institute for Regenerative Medicine (CIRM) entitled *"Tissue Engineered Recellularized Laryngotracheal Implants"*

Dennis J. Hartigan-O'Connor, M.D., Ph.D., received a two-year grant from California HIV/AIDS Research Program titled *"Reservoir Depletion Combined with ART for Functional Cure"*

Dennis Hartigan-O'Connor, M.D., Ph.D. received a 2-year NIH R21 grant titled *"Effective Lethal Agents for CCR5-Expressing Cells"*

Erin Kinnally, Ph.D., received a one-year grant from National Institute of Child Health and Human Development titled *"Epigenetics and the Transgenerational Effects of Early Stress"*

Gerald Lipshutz, UCLA, and co-PI **Alice Tarantal**, Ph.D., received a one-year NIH grant entitled *"Immunologic Aspects of In Utero or Neonatal AAV-Based Gene Therapy"*

Emily S. Rothwell, doctoral student, has received a two-year award from the Bay Area Predoctoral Training Consortium in Affective Science National Institute of Mental Health.

R. Jude Samulski, Ph.D., of the University of North Carolina, Chapel Hill, and **Alice Tarantal**, Ph.D., received a five-year grant from the National Institutes of Health entitled *"Neutralizing Antibody & AAV FIX Gene Therapy"*

Alice Tarantal, Ph.D., received an equipment grant from the NIH entitled *"Nonhuman Primate IVIS Spectrum Imaging System"*

Koen K. Van Rompay, D.V.M., Ph.D., received a one-year award in collaboration with Dan Granoff, M.D., of Children's Hospital Research Center at Oakland, CHORI, entitled *"An Engineered Meningococcal OMV Vaccine for Africa Against All Capsular Groups"*

Koen K. Van Rompay, D.V.M., Ph.D., received a one-year grant from ImmunoScience, Inc., titled *"Safety of nef-deleted SIV in SIV-infected macaques"*

Publications, cont'd

Hennessy MB, McCowan B, Jiang J, and Capitanio JP. Depressive-like behavioral response of adult male rhesus monkeys during routine animal husbandry procedure. Front Behav Neurosci 8:309. 2014. PMCID: PMC4159029

Hirao LA, Grishina I, Bourry O, Hu WK, Somrit M, Sankaran-Walters S, Gaulke CA, Fenton AN, Li JA, Crawford RW, Chuang F, Tarara R, Marco ML, Bäumler AJ, Cheng H, and Dandekar S. Early mucosal sensing of SIV infection by paneth cells induces IL-1β production and initiates gut epithelial disruption. PLoS Pathog 2014 Aug 28;10(8):e1004311. doi: 10.1371/journal.ppat. 1004311. PMCID: PMC4148401

Jiang G, and Dandekar S. Targeting NF-κB signaling with protein kinase C agonists as an emerging strategy for combating HIV latency. AIDS Res Hum Retroviruses. 2014 Oct 6. [Epub ahead of print]

Jiang G, Mendes EA, Kaiser P, Sankaran-Walters S, Tang Y, Weber MG, Melcher GP, Thompson GR 3rd, Tanuri A, Pianowski LF, Wong JK, and Dandekar S. Reactivation of HIV latency by a newly modified Ingenol derivative via protein kinase Cδ-NF-κB signaling. AIDS. 2014 Jul 17;28(11):1555-66. doi: 10.1097/QAD.0000000000000289. PMC Journal-in-Progress

Kang C, Huang Y, and Miller CJ. A discrete-time survival model with random effects for designing and analyzing repeated low-dose challenge experiments. Biostatistics. 2014 Sep 3. pii: kxu040. [Epub ahead of print] PMC Journal-in-Progress

Kinnally EL. Epigenetic plasticity following early stress predicts long-term health outcomes in rhesus macaques. Am J Phys Anthro, 6 Aug 2014 doi: 10.1002/ajpa.22565 PMC Journal-in-Progress

Lemoy MJ, Summers L, and Colagross-Schouten, A. Clinical allograft of a calcaneal tendon in a rhesus macaque (*Macaca mulatta*). J Am Assoc Lab Animal Sci 53(5):523-7, 2014. PMCID: PMC4181695

Li Y, Lin TY, Luo Y, Liu Q, Xiao W, Guo W, Lac D, Zhang H, Feng C, Wachsmann-Hogiu S, Walton JH, Cherry SR, Rowland DJ, Kukis D, Pan C, and Lam KS. A smart and versatile theranostic nanomedicine platform based on nanoporphyrin. Nat Commun 5:4712, 2014. PMCID: PMC4145614

Linz B, Windsor HM, McGraw JJ, Hansen LM, Gajewski JP, Tomsho LP, Hake CM, Solnick JV, Schuster SC, and Marshall BJ. A mutation burst during the acute phase of *Helicobacter pylori* infection in humans and rhesus macaques. Nat Commun, 2014 Jun 13;5:4165. doi: 10.1038/ncomms5165. PMC Journal-in-Progress

Machado CJ, Whitaker AW, Smith SEP, Patterson PH and Bauman MD. Maternal immune activation in nonhuman primates alters social attention in juvenile offspring. Biol Psych, doi: 10.1016/j.biopsych. 2014. 07.035. PMC Journal-in-Progress

Mendoza A, Ng J, Bales KL, Mendoza SP, George DA, Smith DG, Kanthaswamy S. Population genetics of the California National Primate Research Center's (CNPRC) *Callicebus cupreus* colony. Primates. 2014 Sep 2. [Epub ahead of print] PMC Journal-in-Progress

Mooney JP, Butler BP, Lokken KL, Xavier MN, Chau JY, Schaltenberg N, Dandekar S, George MD, Santos RL, Luckhart S, and Tsolis RM. The mucosal inflammatory response to non-typhoidal Salmonella in the intestine is blunted by IL-10 during concurrent malaria parasite infection. Mucosal Immunol. 2014 Nov;7(6):1302-11. doi: 10.1038/mi.2014.18. Epub 2014 Mar 26. PMCID: PMC4177018

Nicol LE, O'Brien TD, Dumesic DA, Tarantal AF, and Abbott DH. Abnormal infant islet morphology precedes insulin resistance in PCOS-like monkeys. PLoS One 9:e106527, 2014. PMCID: PMC4160158

North TW, Villalobos A, Hurwitz SJ, Deere JD, Higgins J, Chatterjee P, Tao S, Kauffman RC, Luciw PA, Kohler JJ, and Schinazi RF. Enhanced antiretroviral therapy in rhesus macaques improves RT-SHIV viral decay kinetics. Antimicrob Agents Chemother. 2014 Jul;58(7):3927-33. doi: 10.1128/AAC.02522-14. Epub 2014 Apr 28. PMCID: PMC4068512

Ottolini B, Hornsby MJ, Abujaber R, Macarthur JA, Badge RM, Schwarzacher T, Albertson DG, Bevins CL, Solnick JV, and Hollox EJ. Evidence of convergent evolution in humans and macaques supports an adaptive role for copy number variation of the β-defensin-2 gene. Genome Biol Evol. 2014 Oct 27. pii: evu236. [Epub ahead of print] PMC Journal-in-Progress

Peretz J, Vrooman L, Ricke WA, Hunt PA, Ehrlich S, Hauser R, Padmanabhan V, Taylor HS, Swan SH, VandeVoort CA, and Flaws JA. Bisphenol A and reproductive health: update of experimental and human evidence, 2007-2013. Environ Health Perspect 122:775-786, 2014. PMCID: PMC4123031

Phillips KA, Bales KL, Capitanio JP, Conley A, Czoty PW, Hart BA, Hopkins WD, Hu SL, Miller LA, Nader MA, Nathanielsz PW, Rogers J, Shively CA, and Voytko ML. Why primate models matter. Am J Primat 76; 801-827, 2014 PMCID: PMC4145602

Qureshi H, Genescà M, Fritts L, McChesney MB, Robert-Guroff M, and Miller CJ. Infection with host-range mutant adenovirus 5 suppresses innate immunity and induces systemic CD4+ T cell activation in rhesus macaques. PLoS One. 2014 Sep 9; 9(9):e106004. doi: 10.1371/journal.pone.0106004. 2014. PMCID: PMC4159191

Ren S, Yang Y, and Cherry SR. Effects of reflector and crystal surface on the performance of a depth-encoding PET detector with dual-ended readout. Med Phys 41:072503, 2014. PMCID: PMC4187348

Ren D, Chin KR, French JA. Molecular Variation in AVP and AVPR1a in New World Monkeys (Primates, Platyrrhini): Evolution and Implications for Social Monogamy. PLoS One. Oct 31, 2014 doi: 10.1371/journal.pone.0111638.

Schmall JP, Roncali E, Berg E, Viswanath V, Du J, and Cherry SR. Timing properties of phosphor-coated polished LSO crystals. Phys Med Biol 59:N139-151, 2014. PMC Journal-in-Progress

Smith PD, Shimamura M, Musgrove LC, Dennis EA, Bimczok D, Novak L, Ballestas M, Fenton A, Dandekar S, Britt WJ, and Smythies LE. Cytomegalovirus enhances macrophage TLR expression and MyD88-mediated signal transduction to potentiate inducible inflammatory responses. J Immunol. 2014 Oct 29. pii: 1302608. [Epub ahead of print] PMC Journal-in-Progress

Stewart JM, Tarantal AF, Chen Y, Appleby NC, Fuentes TI, Lee CC, d'Apice AJ, Cowan PJ, and Kearns-Jonker M. Anti-non-Gal-specific combination treatment with an anti-idiotypic Ab and an inhibitory small molecule mitigates the xenoantibody response. Xenotransplantation 21:254-266, 2014. PMCID: PMC4056685

Stewart JM, Tarantal AF, Hawthorne WJ, Salvaris EJ, O'Connell PJ, Nottle MB, d'Apice AJ, Cowan PJ, and Kearns-Jonker M. Rhesus monkeys and baboons develop clotting factor VIII inhibitors in response to porcine endothelial cells or islets. Xenotransplantation 21:341-352, 2014. PMCID: PMC4056685

Tarantal AF and Berglund L. Obesity and lifespan health – Importance of the fetal microenvironment. Nutrients 6:1725-1736, 2014. PMCID: PMC4011063

Verhoeven D, George MD, Hu W, Dang AT, Smit-McBride Z, Reay E, Macal M, Fenton A, Sankaran-Walters S, and Dandekar S. Enhanced innate antiviral gene expression, IFN-α, and cytolytic responses are predictive of mucosal immune recovery during simian immunodeficiency virus infection. J Immunol. 2014 Apr 1;192(7):3308-18. doi: 10.4049/jimmunol.1302415. Epub 2014 Mar 7.

Vaccari M, Fenizia C, Ma ZM, Hryniewicz A, Boasso A, Doster MN, Miller CJ, Lindegardh N, Tarning J, Landay AL, Shearer GM, and Franchini G. Transient increase of interferon-stimulated genes and no clinical benefit by chloroquine treatment during acute simian immunodeficiency virus infection of macaques. AIDS Res Hum Retroviruses. 2014 Apr;30(4):355-62. doi: 10.1089/AID.2013.0218. Epub 2013 Dec 24. PMCID: PMC3976588

Vom Saal FS, VandeVoort CA, Taylor JA, Welshons WV, Toutain PL, and Hunt PA. Bisphenol A (BPA) pharmacokinetics with daily oral bolus or continuous exposure via silastic capsules in pregnant rhesus monkeys: Relevance for human exposures. Reprod Toxicol 45:105-116, 2014. PMCID: PMC4035044

Weinstein TAR, Bales KL, Maninger N, Hostetler CM, and Capitanio JP. Early involvement in friendships predicts later plasma concentrations of oxytocin and vasopressin in juvenile rhesus macaques (*Macaca mulatta*). Front Behav Neurosci, 8: 295. doi: 10.3389/fnbeh.2014.00295. 2014. PMCID: PMC4147354

Teamwork

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 research:

• ***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).

Photo: K. West

Landscaping crews from UC Davis work to beautify our grounds.

• ***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

'Gold' in a Mountain of Monkey Gravel

Primate Services works with campus to create solutions

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

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 1,840 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 mountainous obstacle to reaching UC-wide goals of zero waste by the year 2020. Here's how they are solving the problem.

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

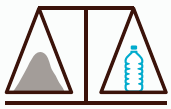
Dallas Hyde, Ph.D. '76, professor and former director of the California National Primate Research Center

Jennifer Short '82, assistant director of colony management and research services at the primate center

Mike Fan, M.S. '99, manager of the wastewater treatment plant. Fan oversees a team that designed, tested and refined the device—apprentices Kelly Cowden and Servando Jimenez and their supervisor, Brad Butterfield.

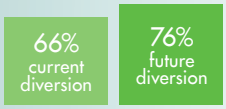
"This was collaboration in the best sense with everyone working toward a common goal," said **David Phillips** '88, who oversees the wastewater plant as utilities director.

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**.

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



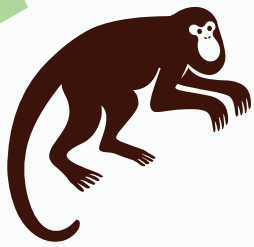
Recycling gravel will bring UC Davis' overall diversion rate to **76 percent**.

THE GRAVEL–WASTEWATER

Soiled gravel is brought from the primate center to be washed.

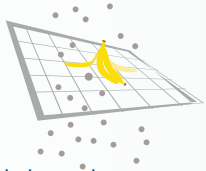
Washing gravel

After trial and error, a team at the wastewater treatment plant devised a system that uses parts from a cement mixer and gold-mining equipment to clean the gravel with reclaimed water.



Clean gravel, if it tests virus-free, will be reused at the primate center.

1 Soiled gravel is put through a screen to filter out large chunks of

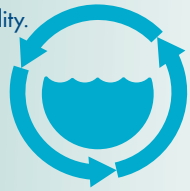


2 The gravel soaks overnight in lightly treated water.

3 The gravel is run through a trommel for final cleaning, similar to gold mining.

Lightly treated water from the wastewater plant is used to wash the gravel.

IT'S NOT ONLY ABOUT GRAVEL: UC Davis' wastewater plant relies on microbes as part of the sanitizing process. Organic matter from the monkey gravel helps keep the digesting bacteria—and the treatment plant—in top working order during the summer and holidays when fewer people are around to keep it flush. "That's another great part of this story—organics going somewhere that they can be helpful instead of detrimental," said Camille Kirk, assistant director of sustainability.



Water runs back to the start of the wastewater treatment

Graphic courtesy of UC Davis Magazine

Translational Highlights

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.

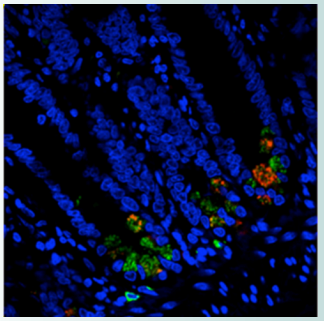
The biology behind this breakdown in the integrity of the gut barrier has been well studied, but what happens before this cascade of events was not understood until the following research study was conducted at the CNPRC at UC Davis.

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 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 appeared to respond to the virus by producing interleukin-1β, an important mediator of the inflammatory response.



Within 2 days of HIV invasion in the gut, Paneth cells (green) produce IL-1β (red), causing inflammation and compromising the integrity of the protective epithelial intestinal layer.

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 can be intervened by the targeted probiotic bacteria" states Dr. Dandekar.

However, the findings also discovered unintended consequences that an *L. plantarum* probiotic therapeutic adjuvant 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.

Hirao LA, Grishina I, Bourry O, Hu WK, Somrit M, Sankaran-Walters S, Gaulke CA, Fenton AN, Li JA, Crawford RW, Chuang F, Tarara R, Marco ML, Bäumler AJ, Cheng H, and Dandekar S. Early mucosal sensing of SIV infection by paneth cells induces IL-1β production and initiates gut epithelial disruption. PLoS Pathog 2014 Aug 28;10(8). PMCID: PMC4148401

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