Scientific Report

TEXAS BIOMEDICAL
RESEARCH INSTITUTE

Enhancing lives through discovery℠

Board of Trustees

EXECUTIVE COMMITTEE

Mr. Richard T. Schlosberg III, *Chairman*
(Retired) Publisher and CEO, Los Angeles Times

Mr. John E. Newman, Jr., *Vice Chairman*
Principal, Newman Brothers

Dr. James "Jamo" Rubin, *Vice Chairman*
Chief Executive Officer, TAVHealth

Mr. James B. Smith, Jr., *Secretary*
Chairman, Cox Smith Matthews Inc.

Mr. John R. Hurd
Chief Executive Officer, Hurd Enterprises, Ltd.

Mrs. Abigail G. Kampmann
Chief Executive Officer, Principle Auto

Mr. John C. Kerr
Principal, Moorman Kerr Interests

Mr. Lewis J. Moorman III
Investor

Mrs. Marsha M. Shields
President, McCombs Foundation

TRUSTEES

Mr. Rex Amini
Managing Director,
Sage Energy Co.

Mr. Edward H. Austin, Jr.
Principal, Austin Family Investments

Mr. Richard N. Azar II
General Partner, Sezar Energy, L.P.

Mr. Craig Boyan
Chief Operating Officer, H-E-B

Mr. J. Bruce Bugg, Jr.
Chairman and CEO,
Argyle Investment Co., LLC

Mr. Robert M. Cavender
President, Cavender Auto Group

Mrs. Phyllis Slick Cowell
President, Slick Enterprises

Mrs. Barbara B. Dreeben
President, Postal Addvantage

Mr. Walter Embrey
Chairman, Embrey Partners, Ltd.

Mr. John W. Feik
CEO, Feik Enterprises LLC

Mrs. Emory Alexander Hamilton
Partner, Groves Alexander

Mrs. Ashley Hixon
Hixon Family Office

Mr. Richard Kardys
Wealth Advisor Senior Officer,
Frost Bank

Mr. William R. Klesse
Chairman of the Board,
Valero Energy Corporation

Mrs. Carolyn H. Labatt
President and CEO,
Computer Solutions

Mr. Mark Pitman Mays
Principal, Rocking M Capital

Mr. Joe C. McKinney
Vice Chairman,
Broadway National Bank

Mr. William G. Moll
(Retired) President & GM, KLRN

Mr. Lew Moorman IV
Entrepreneur

Dr. Dacia Napier
Radiologist

Mr. Charles Urschel Slick
Partner, Slick Enterprises

Mr. John B. Zachry
Chairman and CEO,
Zachry Holdings, Inc.

TRUSTEES EMERITUS

Dr. Ronald K. Calgaard, Ph.D.
Chairman, Ray Ellison
Grandchildren Trust
The Abbey

Mr. Rugeley Ferguson
Investor/Rancher

Mr. Tom C. Frost
Chairman Emeritus, Frost Bank

Mr. James W. Gorman, Jr.
Investor/Rancher

Mr. William E. Greehey
Chairman, NuStar Energy, L.P.

Mr. George C. Hixon
Investor/Rancher

Mr. B. D. Holt
Chairman, Holt Companies

Mrs. Betty Kelso
Investor/Rancher

Mr. Milton B. Lee
(Retired) CEO, CPS Energy

Mr. B. J. McCombs
Chairman, McCombs Enterprises

Mr. Edward E. Whitacre, Jr.
Chairman Emeritus, AT&T

SPECIAL TRUSTEES

Mr. Adam L. Hamilton
President, Southwest
Research Institute

Dr. Andrea Giuffrida
(on behalf of Dr. William L. Henrich)
Vice President for Research and
Interim Associate Professor,
University of Texas Health
Science Center at San Antonio

Dr. Ricardo Romo
President, University of Texas
at San Antonio

HONORARY TRUSTEE

Dr. John P. Howe III
President/CEO, Project HOPE

EX-OFFICIO TRUSTEE

Ms. Jordan Arriaga
President, Founder's Council

Mr. John V. McLaughlin
President, The Argyle

Ms. Amanda Bezner
President, Texas Biomedical Forum

Overview

The Texas Biomedical Research Institute was founded in 1941 by Tom Slick as a nonprofit scientific institution devoted specifically to biomedical research. It has become one of the world's leading independent research institutions dedicated to improving the health of our global community through innovative research on the detection, cause, prevention, cure and eradication of disease.

At Texas Biomed, scientists are empowered to discover tomorrow's cures. Texas Biomed's 200-acre campus with 550,000 square feet of science facilities allows 60 doctoral scientists and 350 employees to unravel the mysteries of chronic and infectious diseases through innovative thinking, creative problem solving and cutting-edge technologies. We know today's discoveries can become tomorrow's cures. This work is possible thanks to an annual budget of $50 million and an endowment of approximately $120 million, operated and directed by a 35-member Board of Trustees.

The Institute is a recognized leader in infectious diseases, the development of nonhuman primate models for complex human diseases, and complex disease genetics. The Department of Genetics uniquely combines genomics, proteomics, metabolomics, computational analysis, and stem cell technologies toward the study of chronic diseases, including cardiovascular, metabolic and neurological disorders.

The Department of Virology & Immunology also operates the Nation's only privately owned Animal Biosafety Level 4 (ABSL-4) maximum containment laboratory that enables the study of deadly pathogens without currently available treatments or vaccines.

Texas Biomed is the host institution for the Southwest National Primate Research Center (SNPRC), one of only seven such centers in the country. SNPRC provides broad services in primate research with specialized technologies, capabilities and primate resources, many of which are exclusive to the SNPRC.

These resources uniquely position the Institute to tackle the challenges of 21st Century research. A few major research highlights from 2015 include:

- Findings on the mechanism by which Ebola virus infects a cell and the discovery of a promising drug therapy candidate was featured on the cover of *Science* in February. Dr. Robert Davey, Chair of the Department of Immunology & Virology, discovered that a small molecule called Tetrandrine (derived from an Asian herb) can inhibit infection of human white blood cells in vitro or petri dish experiments and prevented Ebola virus disease in mice.
    - Yasuteru Sakurai, Andrey A. Kolokoltsov, Cheng-Chang Chen, Michael W. Tidwell, William E. Bauta, Norbert Klugbauer, Christian Grimm, Christian Wahl-Schott, Martin Biel, Robert A. Davey. **Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment.** *Science*, 2015 doi: 10.1126/science.1258758
- Scientists in the Department of Genetics were part of a team of researchers developing a new tool in the fight against malaria. They created a more efficient method to produce genetic crosses between the protozoan parasites causing malaria which will greatly increase understanding of malaria drug resistance. Understanding drug resistance could eventually lead to more effective treatment and potentially better drugs. This work was published as a cover story in the July 1st edition of *Nature Methods*. The study was led by the Centers for Infectious Disease Research (Seattle) in partnership with the University of Notre Dame.
    - Ashley M Vaughan, Richard S Pinapati, Ian H Cheeseman, Nelly Camargo, Matthew Fishbaugher, Lisa A Checkley, Shalini Nair, Carolyn A Hutyra, François H Nosten, Timothy J C Anderson, Michael T Ferdig, Stefan H I Kappe. ***Plasmodium falciparum* genetic crosses in a humanized mouse model**. *Nature Methods*. 12, 631–633 (2015) doi:10.1038/nmeth.3432.
- Data from a study by Dr. Ruth Ruprecht published in the journal *Vaccine* provided a proof of concept for a two-pronged approach to preventing HIV acquisition. The study examined vaccination generating a mucosal immune response, as well as a systemic antibody response and found that this approach generated a 100 percent protection in nonhuman primates. Further studies are ongoing.
    - Anton M. Sholukh, Jennifer D. Watkins, Hemant K. Vyas, Sandeep Gupta, Samir K. Lakhashe, Swati Thorat, Mingkui Zhou, Girish Hemashettar, Barbara Bachler, Donald N. Forthal, François Villinger, Quentin J. Sattentau, Robin A. Weiss, Gloria Agatic, Davide Corti, Antonio Lanzavecchia, Jonathan Luke Heeney, Ruth M. Ruprecht. **Defense-in-depth by mucosally administered anti-HIV dimeric IgA2 and systemic IgG1 mAbs: complete protection of rhesus monkeys from mucosal SHIV challenge.** *Vaccine*. 2015 Apr 21; 33(17):2086-95. doi: 10.1016/j.vaccine.2015.02.020.

In an environment that fosters collaboration, encourages curiosity and creativity and rewards innovation, scientists at Texas Biomed are dedicated to enhancing lives through discovery.

The following report highlights the Institute's top level scientists and their area of expertise. Researchers are listed alphabetically and identified by their area of research in the subhead of each biographical page. Also included are the veterinarians and behavioral staff critical to the operations of Texas Biomed and the Southwest National Primate Research Center. To contact one of the Institute's researchers or learn more about Texas Biomed, please visit the Institute's website at www.txbiomed.org.

OFFICERS OF THE INSTITUTION

President and Chief Executive Officer
Robert Gracy, Ph.D.

Vice President for Finance and Administration, Chief Financial Officer
Keith Davis

SENIOR ADMINISTRATORS

Vice President, Human Resources
John Barnes

Chief Information Officer
Brian Bounds

Vice President for Institutional Advancement and Public Relations
Corbett Christie

DEPARTMENT OF GENETICS

Chair
Michael Olivier, Ph.D.

Vice Chair
Laura Cox, Ph.D.

Scientists
Timothy Anderson, Ph.D.
Anthony Comuzzie, Ph.D.

Associate Scientist
Melanie Carless, Ph.D.

Assistant Scientist
Ian Cheeseman, Ph.D.

Staff Scientists III
Shelley Cole, Ph.D.
John Kent Jr., Ph.D.

DEPARTMENT OF VIROLOGY AND IMMUNOLOGY

Chair
Robert Davey, Ph.D.

Vice Chair
Luis D. Giavedoni, Ph.D.

Scientists
Robert Lanford, Ph.D.
Jean Patterson, Ph.D
Ruth Ruprecht, M.D., Ph.D.

Associate Scientists
Ricardo Carrion, Jr., Ph.D.
Marie-Claire Gauduin, Ph.D.
Anthony Griffiths, Ph.D.
Andrew Hayhurst, Ph.D.

SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

Director
Robert Lanford, Ph.D.

Associate Director of Research
Suzette Tardif, Ph.D.

Associate Director for Veterinary Resources and Research Support
John Bernal, D.V.M.

Assistant Director of Research Resources
Karen Rice, Ph.D.

Associate Scientists
Tiziano Barberi, Ph.D.
Marcel Daadi, Ph.D.

Staff Scientists III
Raul Bastarrachea, M.D.
Corrine Lutz, Ph.D.
Jerilyn Pecotte, Ph.D.

Veterinarians
Kathleen Brasky, V.M.D.
Edward Dick, Jr., D.V.M.
Patrice Frost, D.V.M.

Associate Veterinarians
Melissa De La Garza, D.V.M.
Michael Owston, D.V.M.

Assistant Veterinarian
Shannan Hall-Ursone, D.V.M.

TEXAS BIOMEDICAL RESEARCH INSTITUTE℠

Enhancing lives through discovery℠

February 2016

TIMOTHY ANDERSON, PH.D.

SCIENTIST, GENETICS

RESEARCH FOCUS

Parasitic diseases still plague broad swaths of the world's developing countries, reducing childhood survival rates and stunting economic growth. However, genome sequence data for the pathogens involved and funding from various organizations give new hope of controlling or even eliminating these diseases. Dr. Anderson focuses on the genetic basis and evolution of biomedically important traits in two of the most important human groups of parasites:

- Malaria parasites (~655,000 deaths per year)
- Parasitic blood fluke (*Schistosoma* species) responsible for schistosomiasis (~200,000 deaths per year)

Dr. Anderson has 30 years of experience working in parasitology.

INSIDE THE LAB

Malaria infects around 300 million people each year, killing ~655 thousand people. No vaccine exists, and by now, parasite resistance to all five classes of antimalarial drugs has been reported. We use several different strategies to identify genes that underlie drug resistance and to better understand drug resistance evolution. Our lab closely collaborates with clinicians working on the Thailand-Myanmar border and with researchers in Malawi.

- As the malaria genome is relatively small, whole genome sequence information from populations of parasites can be studied. We are using genomic analysis of field-collected parasites and genetic crosses conducted in humanized mice to identify drug resistance genes and better understand drug resistance evolution.
- Change in gene copy number is an important and understudied cause of resistance in pathogens. By examination of copy number variation, we have already characterized an important gene involved in drug resistance.
- Gene editing methods using CRISPR/Cas9 now allow us to introduce specific changes to the malaria parasite genome, so we can experimentally investigate the effects of specific mutations.

Using the approaches listed above, we are addressing several fundamental questions about drug resistance evolution: How many times has drug resistance evolved in nature? What genes are involved? What is the role of copy number variation and single nucleotide polymorphisms? What is the rate of mutation? What is the impact of resistance genes on parasite fitness? Answering these questions could help identify drug targets and novel interventions against malaria.

Schistosomiasis is caused by blood flukes (*Schistosoma* spp.). These parasites infect over 270 million people in Africa, South America and Asia, and utilize snail intermediate hosts. The adult worms live in blood vessels, but the eggs cause pathology by lodging in the liver or intestine wall, where granulomas form, resulting in periportal fibrosis and hepatosplenic disease. Schistosomes are rare among human parasites, in that the complete lifecycle can be maintained in the laboratory. Our lab has pioneered the use of genetic crosses between schistosomes in the laboratory for identifying the genetic basis of biomedically important parasite traits. We have used this approach, together with exome sequencing, to identify the precise mutations that underlie oxamniquine resistance, and are now applying the same approach to understand praziquantel resistance, host specificity, parasite virulence, and multiple other important biomedical traits.

The complete parasite lifecycle is maintained at Texas Biomed, using colonies of snail intermediate host, and hamsters or mice in place of humans for the vertebrate stage of the parasite lifecycle. We collaborate closely with Dr. Philip LoVerde at the University of Texas Health Science Center, as well as with colleagues in London (UK), Perpignan (France), Kenya, Uganda, and Brazil.

MAIN TECHNOLOGIES AND METHODS USED

- RNA-Sequencing/Quantitative PCR and RT-PCR
- Single cell genomics/FACs
- SNP genotyping
- Malaria parasite culture and growth assays
- CRISPR/Cas9 gene editing
- Custom exome sequencing (schistosomes)
- Schistosome lifecycle maintenance
- Linkage mapping in experimental crosses

PUBLICATIONS

- Valentim CL, Cioli D, Chevalier FD, Cao X, Taylor AB, Holloway SP, Pica-Mattoccia L, Guidi A, Basso A, Tsai IJ, Berriman M, Carcahlo-Queiroz C, Almeida M, Aguilar H, Frantz D, Hart PJ, LoVerde P, **Anderson TJ**. Genetic and molecular basis of drug resistance and species-specific drug action in schistosome parasites. *Science* 2013; 342:1385-1389. PMC4136436
- Nair S, Miller B, Barends M, Jaidee A, Patel J, Mayxay M, Newton P, Nosten F, Ferdig MT, **Anderson TJ**. Adaptive copy number evolution in malaria parasites. *PLoS Genet* 2008; 4:e1000243. PMC2570623
- Phyo AP, Nkhoma S, Stepniewska K, Ashley EA, Nair S, McGready R, ler Moo C, Al-Saai S, Dondorp A, Lwin KM, Singhasivanon P, Day NP, White NJ, **Anderson TJ**, Nosten F. Emergence of artemisinin-resistant malaria on the western border of Thailand: A longitudinal study. *Lancet* 2012; 379:960-1966. PMC3525980

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/40734139/?sort=date&direction=descending

TIZIANO BARBERI, PH.D.

ASSOCIATE SCIENTIST, SNPRC

RESEARCH FOCUS

Dr. Barberi's research is focused on human pluripotent stem cells (hPSC) and non-human primate pluripotent stem cells (PSC). These cells have great potential for use in cell engineering-based therapies and as a model for early human development.

Dr. Barberi's research group studies the directed differentiation of human pluripotent stem cells and non-human primate stem cells into specific fates. An understanding of the mechanisms of early development is important for our knowledge of human disease because these cells can give rise to all cell types of our body. Dr. Barberi aims to generate hPSC-derived specialized progeny that will be used for drug screening, modeling of diseases, and for pre-clinical applications.

His studies encompass the development of the skeletal muscle system, the retina of the eye and early neural development, specifically:

- Skeletal muscle development and its *in vivo* applications in animal models of muscle disease
- Modeling the development of neural plate border cell populations, cranial placodes, and neural crest
- *In vitro* generation of neural retina cells for eye repair

Dr. Barberi has more than 20 years of experience working in stem cell research.

INSIDE THE LAB

Human pluripotent stem cells (hPSC) encompass human embryonic stem cells (hESC) and human induced-pluripotent stem cells (hiPSC). Human embryonic stem cells (hESCs) are pluripotent cells derived from the inner cell mass of the blastocyst. *In vitro*, these cells display extensive proliferation and the ability to differentiate into derivatives of all three germ layers, resulting in their great potential for use in cell engineering-based therapies and as a model for early human development. Human induced-pluripotent stem cells (hiPSC) are ESC-like cells derived from adult somatic tissues through cellular reprogramming.

We use hESC and hiPSC as an *in vitro* model of cell fate determination and lineage specification, and to obtain specialized cells.

To direct the differentiation of hPSC into the fates of interest, we establish specific culture conditions that combine the use of distinctly coated dishes with a serum-free medium and an appropriate cocktail of growth factors and/or active small molecules. Upon differentiation, we use fluorescence-activated cell sorting (FACS) technology to purify the desired cell populations, an essential prerequisite that provides the basis for the next step: to generate hPSC-derived specialized progeny to be used for drug screening, disease modeling, and pre-clinical applications.

Our studies include the following:

Skeletal muscle development from hPSCs

- Identification and isolation of striated myogenic precursors
- *In vitro* characterization of the precursors and their terminal differentiation into mature myocytes
- Transplantation of PSC-derived muscle precursors into animal models of muscle disease

Modeling the development of neural plate border cell populations, neural crest and cranial placodes

- Differentiation of hPSCs into panplacodal ectoderm
- Differentiation of hPSCs into lens epithelium
- Isolation and purification of lens epithelium
- Derivation of olfactory placode
- Differentiation of olfactory epithelium into olfactory and GDNH neurons

Differentiation of hPSCs into retinal cells

- Optimization of culture conditions for forebrain development
- Role of growth factors/small molecules in inducing retinal cell differentiation
- Differentiation of hPSCs into retina progenitors and specific retinal cell subtypes
- FACS-mediated isolation of retina progenitors
- Transplantation of retina progenitors into animal models of retina degeneration

MAIN TECHNOLOGIES AND METHODS USED

- Fluorescence-activated cell sorting (FACS)
- Analytical flow cytometry
- Tissue culture
- Stem cell differentiation
- PCR
- Western blot
- Immunocytochemistry
- Gene editing (CRISPR)

PUBLICATIONS

- Borchin BE, **Barberi T**. The use of human pluripotent stem cells for the *in vitro* derivation of cranial placodes and neural crest cells. *Curr Top Dev Biol* 2015; 111:497-514. PMID: 25662270
- Mengarelli I, **Barberi T**. Derivation of multiple cranial tissues and lens epithelium-like cells from human embryonic stem cells. *Stem Cells Transl Med* 2013 Feb;2(2): 94-106. PMID:23341438, PMC3659756
- Borchin B, Chen J, **Barberi T**. Derivation and FACS-mediated purification of PAX3+/PAX7+ skeletal muscle precursors from human pluripotent stem cells. *Stem Cell Reports*. 2013; 1(6):620-31. PMID:24371814, PMC3871395

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47974764/?sort=&direction=

RAUL A. BASTARRACHEA, M.D.

STAFF SCIENTIST III, GENETICS AND SNPRC

RESEARCH FOCUS

Dr. Bastarrachea is a Staff Scientist in the SNPRC and the Department of Genetics. His research focuses on the biology and genetics of complex metabolic traits with focus on cardiovascular disease, obesity, and type 2 diabetes. His research has helped to develop and establish the baboon as a non-human primate (NHP) model to study the physiological mechanisms regulating fat tissue metabolism in obesity and diabetes, with a special emphasis on hormone regulation and action.

INSIDE THE LAB

After developing novel sophisticated tracer methods and blood vessel catheterizations to study free fatty acid kinetics in the baboon, we developed a high-fat, high-carbohydrate challenge diet, which showed pronounced and rapid negative effects on a wide range of key metabolic parameters, consistent with the metabolic disruptions seen in humans.

Recently, we established a method of streptozotocin-induced diabetes in conscious tethered baboons. We successfully induced frank diabetes by IV-administering a single dose of streptozotocin safely and without adverse events in conscious tethered baboons. Animals were continuously monitored, using a tether system that allows moment-by-moment monitoring of glucose levels after administration, and continuous intravenous insulin therapy. We described a triphasic response in blood glucose after streptozotocin administration, including a hypoglycemic phase. Hyperglycemia in these animals was associated with low levels of plasma leptin, insulin and C-peptide concentrations, hyperglucagonemia, and elevated non-esterified fatty acids (NEFA) concentrations.

In collaboration with cardiologist Paul Grayburn, M.D. (Director of Cardiology Research, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX), we applied this model to test and implement a state-of-the- art gene-based therapy in the baboon model using a novel gene delivery protocol called UTMD (micro-bubble delivery) for the treatment of type 1 diabetes. We targeted non-viral gene therapy to pancreatic islets using ultrasound targeted microbubble destruction (UTMD) in baboons. Our Preliminary data indicate that gene therapy by UTMD can achieve *in vivo* normalization of the intravenous (IV) glucose tolerance test (IVGTT) curves in streptozotocin-induced diabetic baboons. Immunohistochemistry demonstrated evidence of islet regeneration and restoration of β-cell mass.

This recent work is an extension of earlier studies performed in collaboration with Dr. Ralph A. DeFronzo and the Diabetes Division at UT Health Science Center San Antonio, where we established euglycemic-hyperinsulinemic clamping in baboons, widely considered the gold standard for assessing insulin action *in vivo*.

Fat accumulation in the liver is symptom of a condition called nonalcoholic steatohepatitis (NASH), found in individuals who consume little or no alcohol. Obesity and diabetes are the two strongest risk factors for the development of NASH in humans. We have established stable isotope infusion protocols under the tether system in baboons to measure the relative sources of fats (triglycerides) that are secreted in lipoproteins and stored in the liver.

Overall, we have developed and established a baboon model for the study of diet-induced cardiometabolic syndrome. We have developed tools for detailed physiological characterizations of hormone action, specifically the regulation of fat cell metabolism, and have used the animal model and approaches for a wide range of studies, including dietary intervention studies and gene therapy.

MAIN TECHNOLOGIES AND METHODS USED:

- Euglycemic-hyperinsulinemic clamping in baboons
- Micro-bubble delivery for gene therapy
- Molecular physiology of insulin and adipokines

PUBLICATIONS

- Frost PA, Chen S, Mezzles MJ, Voruganti VS, Nava-Gonzalez EJ, Arriaga-Cazares HE, Freed KA, Comuzzie AG, DeFronzo RA, Kent JW Jr, Grayburn PA, **Bastarrachea RA**. Successful pharmaceutical-grade streptozotocin (STZ)-induced hyperglycemia in a conscious tethered baboon (Papio hamadryas) model. *J Med Primatol* 2015, Aug;44(4):202-17. PMID:26122701
- Chen S, **Bastarrachea RA**, Roberts BJ, Voruganti VS, Frost PA, Nava-Gonzalez EJ, Arriaga- Cazares HE, Chen J, Huang P, DeFronzo RA, Comuzzie AG, Grayburn PA.Successful β cells islet regeneration in streptozotocin-induced diabetic baboons using ultrasound-targeted microbubble gene therapy with cyclinD2/CDK4/GLP1. *Cell Cycle* 2014, Apr 1;13(7):1145-51. PMID:24553120, PMC4013164
- Kamath S, Chavez AO, Gastaldelli A, Casiraghi F, Halff GA, Abrahamian GA, Davalli AM, **Bastarrachea RA**, Comuzzie AG, Guardado-Mendoza R, Jimenez-Ceja LM, Mattern V, Paez AM, Ricotti A, Tejero ME, Higgins PB, Rodriguez-Sanchez IP, Tripathy D, DeFronzo RA, Dick EJ Jr, Cline GW, Folli F. Coordinated defects in hepatic long chain fatty acid metabolism and triglyceride accumulation contribute to insulin resistance in non-human primates. *PLoS ONE* 2011, 6(11): e27617. PMC3220682

A complete list of publications can be found at
www.ncbi.nlm.nih.gov/pubmed/?term=Bastarrachea+RA

JOHN BERNAL, D.V.M.

ASSOCIATE DIRECTOR OF VETERINARY RESOURCES AND RESEARCH SUPPORT, SNPRC

RESEARCH FOCUS

Dr. Bernal oversees all aspects of the SNPRC animal care and use program. He has more than 36 years of experience in laboratory animal care and medicine. To increase the number of certified laboratory animal technicians at Texas Biomed and other institutions, he has developed institution-wide training and certification programs. Dr. Bernal has been integral to developing the SNPRC study process manual that details all of the steps required to complete a study from start to finish. Dr. Bernal oversees and develops standard operating procedures for:

- Comprehensive socialization and environmental enrichment plan
- Preventative medicine program (frequent physicals, TB testing, parasite evaluation, viral testing)
- Veterinary care program
- Aseptic technique
- Management of pain and distress
- Animal enclosure sanitation.

In his role as manager of global primate supplies for a contract research organization (CRO), Dr. Bernal spent more than a decade working in the non-human primate (NHP) breeding/production industry in Asia. As a veterinarian in a CRO, Dr. Bernal was integral to developing a program of modular housing in a GLP facility. He developed technical procedures for use in an NHP toxicology research laboratory and improved the health and care of NHPs imported into the U.S. for use in biomedical research. Import mortalities in the early 1990s were reaching 6-10%, and dropped below 0.5% thanks to these improved practices that remain effective for improving animal welfare in the primate centers in Asia that help provide a high quality biomedical NHP research model.

Dr. Bernal's expertise includes the facilities design and implementation, clinical oversight and management of three large macaque breeding, holding and CDC-registered importation facilities. Positions as Director of Laboratory Animal Medicine and Technical Operations for a GLP NHP contract research organization, General Manager for an NHP supply organization, and Executive Director of Global Primate Supplies for a CRO contribute to his success in his current position as Associate Director of Veterinary Resources and Research Support.

PUBLICATIONS

- Rippy MK, Lee DR, Pearson SL, **Bernal JC**, Kuehl TJ. Identification of rhesus macaques with spontaneous endometriosis. *J Med Primatol* 1996, 25(5):346-55. PMID: 9029399
- Walker MD, Templin MV, **Bernal JC**, Jacobson SB, Gad SC, editor. Animal models in toxicology. 3rd ed. Boca Raton: CRC Press/Taylor & Francis; 2015. Chapter 9, Primates; p.671-762 [book].

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47550513/?sort=date&direction=ascending

KATHLEEN BRASKY, V.M.D.,M.S., DACLAM

VETERINARIAN, SNPRC

RESEARCH FOCUS

Dr. Brasky has been a veterinarian for 28 years and has worked with non human primates in biomedical research for 25 years at Texas Biomed/SNPRC. She has the primary veterinary responsibility for the chimpanzee resource and the marmoset colony and has also worked as a research veterinarian for more than 15 years with a variety of non-human primate species and within all levels of animal biosafety containment.

Her work includes studies on several infectious disease models, the planning of experimental protocols for research with macaques, marmosets and baboons, and providing oversight for technical procedures.

Dr. Brasky is the primary responsible veterinarian for clinical care and research support in the marmoset colonies and participates in collaborative research and training related to marmosets. Marmosets are small non-human primates commonly used in many biomedical disciplines (neuroscience, reproductive biology, infectious disease, behavioral science). The marmoset breeding colony at SNPRC was established in 2004 and has provided animals for a variety of studies ranging from biodefense to diet-induced obesity. Dr. Brasky promotes the use of marmosets in various biocontainment and aging studies, and promotes a healthy population of marmosets available for use in biomedical research.

In addition, Dr. Brasky maintains a small colony of tamarins for use in GB virus-B research (a model for studying hepatitis-C).

She manages the chimpanzee resource by providing the necessary clinical care to this aging colony and designing optimized housing conditions as ethologically appropriate for this species.

Currently, Dr. Brasky is involved in several collaborative simian-human immunodeficiency virus (SHIV) projects that encompass various species of macaques and pediatric macaque models.

MAIN TECHNOLOGIES AND METHODS USED

- Ultrasonography
- Experimental and clinical surgery
- Wireless infusion with implantable pumps
- Bronchoscopy
- Imaging anesthesia support
- Animal model development

PUBLICATIONS

- Bert AA, Drake WB, Quinn RW, **Brasky KM**, O'Brien JE Jr, Lofland GK, Hopkins RA. Transesophageal echocardiography in healthy young adult male baboons (*Papio hamadryas anubis*): Normal cardiac anatomy and function in subhuman primates compared to humans. *Prog Pediatr Cardiol* 2013, Aug 1;35(2):109-120 PMID:24707162, PMC3974204
- Schaal JB, Tran D, Tran P, Osapay G, Trinh K, Roberts KD, **Brasky KM**, Tongaonkar P, Ouellette AJ Selsted. Rhesus macaque theta defensins suppress inflammatory cytokines and enhance survival in mouse models of bacteremic sepsis. *PLoS One* 2012, 7(12):e51337. PMID:23236475, PMC3516535
- Lanford RE, Guerra B, Chavez D, Giavedoni L, Hodara VL, **Brasky KM**, Fosdick A, Frey CR, Zheng J, Wolfgang G, Halcomb RL, Tumas DB. GS-9620, an oral agonist of Toll-like receptor-7, induces prolonged suppression of hepatitis B virus in chronically infected chimpanzees. *Gastroenterology* 2013, Jun;144(7):1508-17. PMID: 23415804, PMC3691056

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/43696068/?sort=date&direction=ascending

MELANIE A. CARLESS, PH.D.

ASSOCIATE SCIENTIST, GENETICS

RESEARCH FOCUS

Dr. Carless works on genetic and epigenetic factors that drive the development and progression of heart disease and mental disorders. Her work aims to advance the current knowledge of epigenetic involvement in complex diseases and understand interactions that influence genetic regulation. This will help to identify novel targets for drug development and better therapeutic intervention.

- Role of DNA methylation on obesity and metabolic syndrome
- Genetic effects on migraine
- Gene expression and DNA methylation changes associated with schizophrenia, bipolar disorder, depression and associated neuropsychiatric traits
- Role of microRNAs and microRNA variants in psychiatric diseases (schizophrenia, bipolar disorder, depression, PTSD, and associated neuropsychiatric traits)
- Effect of microRNAs on gene expression
- Understanding psychiatric disorders through induced pluripotent stem cells

Dr. Carless has more than 15 years of experience working in molecular genetics.

INSIDE THE LAB

Epigenetic mechanisms, such as DNA methylation and microRNA regulation, are now considered significant players in the development of complex diseases, although the integration of these factors with our genetic architecture is not well understood. Our lab studies epigenetic variation that contributes to complex disease development and the role of this variation in the genetic-transcriptomic paradigm.

In collaborative efforts, we generated genome-wide genotyping and gene expression data for the San Antonio Family Study (SAFS) to investigate genes involved in cardiovascular- and psychiatric-related phenotypes. One of our findings implicates a novel genetic region associated with intima-media thickness, a risk factor for cardiovascular disease. We have also generated epigenome-wide DNA methylation profiles in our investigation of metabolic syndrome and related phenotypes within the SAFS, identifying several genes whose DNA methylation levels are associated with diabetes, obesity and dyslipidemia. Further study of the gene TXNIP, crucial for regulation of glucose and lipid homeostasis, suggests its specific role in the onset of diabetes.

Our studies demonstrated the importance of genetic variation in the expression of the *DISC1* gene, a well-known risk gene for schizophrenia and bipolar disorder, and identified variation that influences brain structure, suggesting a mechanism by which the gene may act to influence psychiatric disorders.

Using next-generation sequencing within the SAFS cohort, we identified a potentially novel microRNA, nominally associated with brain structure phenotypes involved in memory. We continue to research the role of microRNAs in psychiatric disease by investigating cohorts involving schizophrenia, bipolar disorder, major depressive disorder and post-traumatic stress disorder.

Other collaborative efforts led to the generation of transcriptional data to identify markers of adiposity, hypertriglyceridemia, cardiovascular disease risk metabolic syndrome, fatty liver disease, migraine, bipolar disorder and schizophrenia.

To determine the functional impact of genetic and epigenetic variation on the development of novel therapeutics and delivery methods, we are conducting pilot studies to establish induced pluripotent stem cell lines and differentiated neuronal cells from adolescents with bipolar disorder. Here we aim to understand potential delivery mechanisms for small biological molecules.

We are also working on establishing new methodologies to study the effect of microRNAs on gene and protein expression on a genome-wide scale.

Many of our recent genetic and epigenetic findings point to the importance of ethnic-specific variation and risk, solidifying the need to study minority cohorts.

MAIN TECHNOLOGIES AND METHODS USED

- Illumina next-generation sequencing — whole genome sequencing, exome sequencing, RNA-Seq, miRNA-Seq, Methyl-Seq
- Pyrosequencing
- Methylation-based PCR
- Microarray analysis
- Transcriptional profiling
- Genotyping
- Cell culture and cell-based assays
- Functional analysis

PUBLICATIONS

- Kos MZ, **Carless MA**, Peralta J, Blackburn A, Almeida M, Roalf D, Pogue-Geile MF, Prasad K, Gur RC, Nimgaonkar V, Curran JE, Duggirala R, Glahn DC, Blangero J, Gur RE, Almasy L. Exome sequence data from multigenerational families implicate ampa receptor trafficking in neurocognitive impairment and schizophrenia risk. *Schizophr* Bull 2015, Sep 24. Epub ahead of print. PMID: 26405221
- Kulkarni H, Kos MZ, Neary J, Dyer TD, Kent JW Jr, Göring HHH, Cole SA, Comuzzie AG, Almasy L, Mahaney MC, Curran JE, Blangero J, **Carless MA**. Novel epigenetic determinants of type 2 diabetes in Mexican-American families. *Hum Mol Genet* 2015, 24(18):5330-44. PMID: 26101197, PMC4550817
- **Carless MA**, Glahn DC, Johnson MP, Curran JE, Bozaoglu K, Dyer TD, Winkler AM, Cole SA, Almasy L, MacCluer JW, Duggirala R, Moses EK, Göring HHH, Blangero J. Impact of DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Mol Psychiatry* 2011, 16(11):1096-104. PMID: 21483430, PMC3135724

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/1VyBtdAGsH4ky/bibliography/48004124/public/?sort=date&direction=ascending

RICARDO CARRION, JR., PH.D.

ASSOCIATE SCIENTIST, VIROLOGY & IMMUNOLOGY,
BSL-4 LABORATORY ASSOCIATE DIRECTOR

RESEARCH FOCUS

Dr. Carrion's lab aims to advance the vaccine and therapy development specifically for hemorrhagic fever, an illness caused by viruses from distinct families, many of which have no cure, and for which no vaccines are available. The team uses the maximum containment biosafety level 4 (BSL-4) laboratory to safely study those pathogens.

- Ebola virus, Marburg virus
- Common marmoset nonhuman primate infectious disease models
- Advanced development of vaccines for hemorrhagic fever viruses
- New detection methods for bioterror agents

Dr. Carrion has more than 15 years of experience in microbiology and parasitology.

INSIDE THE LAB

Filoviruses, such as Ebola virus and Marburg virus, are examples of highly lethal agents that induce hemorrhagic fever with a mortality rate of up to 90 percent. These viruses have also been responsible for an 88 percent decline in the world's chimpanzee populations since 2003.

In support of filovirus vaccine development, we have developed the common marmoset as a nonhuman primate model for Ebola and Marburg virus disease. We have shown that marmosets, small new world monkeys weighing less than 400 grams, exhibit disease effects similarly to humans, and can serve as a small nonhuman primate model for filovirus-induced hemorrhagic fever. Identification of this rodent-sized nonhuman primate model is so important because marmosets are more predictive of therapeutic efficacy than traditional small animal models.

Most recently, we have been awarded contracts to test the efficacy of several vaccine platforms against filoviruses, including multivalent virus like particle (VLP) vaccines, adeno-vectored vaccines, and modified vaccinia ankara (MVA) vaccines. Most have shown efficacy in smaller animal models and will be validated in nonhuman primate models of disease at Texas Biomed. Several vaccine candidates that were previously tested with success at Texas Biomed are now part of human clinical safety trials.

Our lab has shown that two drugs available for leukemia treatment can also block Ebola replication *in vitro*. Replication of the highly pathogenic Ebola virus strain Zaire, responsible for the recent (2014-15) Ebola virus epidemic in West Africa, was inhibited by c-Abl1-specific siRNAs or by the Abl-family inhibitor nilotinib. This indicates that c-Abl regulates budding or release of filoviruses, offering a potential new target for antiviral therapy.

In our efforts to discover new detection methods for bioterror agents, we recently teamed up with a local biotechnology company to test an Handheld Aptamer-Magnetic Bead-Quantum Dot Sensor for Crimean Congo Hemorrhagic Fever (CCHF), a tick-borne disease causing hemorrhagic fever in eastern Europe, Asia, India and Africa, with hospitalized patient fatality rates ranging from 9 to 50 percent.

Additionally, we collaborated with researchers to develop an optofluidic analysis system for amplification-free, direct detection of Ebola infection. This technology uses on-chip fluorescence detection for biosensing applications.

To advance our development of therapeutic antibodies for treatment of Ebolavirus disease, we have recently teamed with BARDA, the Biomedical Advanced Research and Development Authority.

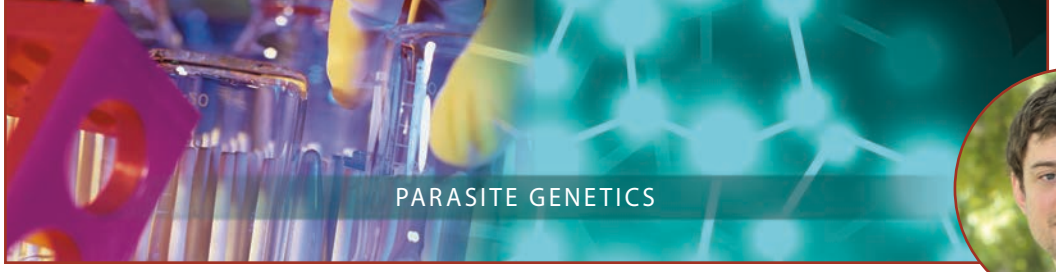
MAIN TECHNOLOGIES AND METHODS USED

- BSL-4 laboratory research
- Filovirus macaque models
- Marmoset infectious disease models

PUBLICATIONS

- Alfson KJ, Avena LE, Beadles MW, Staples H, Nunneley JW, Ticer A, Dick EJ Jr, Owston MA, Reed C, Patterson JL, **Carrion R Jr**, Griffiths A. Particle-to-PFU ratio of Ebola virus influences disease course and survival in cynomolgus macaques. *J Virol* 2015; 89(13):6773-81. PMID: 25903348, PMC4468478
- **Carrion R Jr**, Ro Y, Hoosien K, Ticer A, Brasky K, de la Garza M, Mansfield K, Patterson JL. A small nonhuman primate model for filovirus-induced disease. *Virology* 2011, 420: 117-124, PMID: 21959017, PMC3195836
- Madrid PB, Chopra S, Manger ID, Gilfillan L, Keepers TR, Shurtleff AC, Green CE, Iyer LV, Dilks HH, Davey RA, Kolokoltsov AA, **Carrion R Jr**, Patterson JL, Bavari S, Panchal RG, Warren TK, Wells JB, Moos WH, Burke RL, Tanga MJ. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. *PLoS One* 2013, 8(4):e60579. doi: 10.1371 PMID: 23577127, PMC3618516

A complete list of publications can be found at
www.ncbi.nlm.nih.gov/pubmed/?term=Carrion+R+Jr



IAN CHEESEMAN, PH.D.

ASSISTANT SCIENTIST, GENETICS

RESEARCH FOCUS

The Cheeseman laboratory uses genomic and computational approaches to characterize the complexity of malaria infections, the evolution of drug resistance, and the rate and spectrum of adaptive mutations in the malaria parasite genome.

- Study complex malaria infections with single cell genomics approaches in those malaria parasites that are most deadly *(Plasmodium falciparum)* and most prevalent *(Plasmodium vivax)*
- Investigate the emergence and spread of drug resistance in malaria parasites

Thanks to his expertise, Dr. Cheeseman was recently invited to join the Pf3K consortium, an international effort to characterize genetic variation and the impact of natural selection in over 3,000 directly sequenced malaria parasite genomes.

Dr. Cheeseman has 10 years of experience working in parasitology.

INSIDE THE LAB

Malaria infects around 300 million people each year, killing nearly 655,000 people. Resistance to all five classes of antimalarial drugs is known, emphasizing the need to better understand drug resistance, infection complexity, and evolution of adaptive parasite mutations. We have developed methods to isolate individual malaria parasites of *P. falciparum*, and *P. vivax*, and we are using these tools to understand how complex malaria infections are — a major black box in malaria epidemiology.

Malaria infections frequently contain multiple distinct genetic backgrounds. This complexity challenges standard genetic analysis and prevents direct haplotype capture. The single cell sequencing approach we developed comprises isolation of individual malaria parasites by cell sorting, amplification of genetic material using whole genome amplification, and whole genome sequencing.

Bioinformatic approaches allow us to identify genetic variation from next generation sequencing data. The extreme nucleotide bias of the malaria parasite genome (~80% AT-rich) requires extensive optimization and validation of analytical tools. These pipelines have become integral to our projects to understand parasite genetic variation. The genome of *P. falciparum* poses a particularly challenging target for genomics. It is highly repetitive and the most AT-rich genome sequenced to date. My lab has developed methods for accurate scoring of genetic variants from microarray and next generation sequencing platforms for *P. falciparum*. We apply these methods to population-scale datasets to identify the targets of natural selection and map the emergence of drug resistance.

Drug resistance to artemisinin, currently the global front-line treatment for malaria infections, was first observed in 2004, and has rapidly spread through South-East Asia. Given that the loss of previous anti-malarial drugs has resulted in a substantial increase in mortality, it is imperative that we rapidly characterize drug resistance. Using population genetic methods, we identified a region of chromosome 13 in the parasite genome as a major determinant of artemisinin resistance. This was subsequently confirmed as the *kelch* gene. Employing this system, we have developed a method to rapidly map resistance by pooled sequencing of resistant and sensitive parasites. Our approach led to direct implication of *kelch* in a cost-effective and accurate way and opens the door for rapid identification.

MAIN TECHNOLOGIES AND METHODS USED

- Single cell genomics/transcriptomics
- Illumina DNA sequencing
- RNA-Seq
- Fluorescence-Activated Cell Sorting (FACS)
- Malaria parasite culture and growth assays
- Linkage mapping in experimental crosses
- Genome-wide association studies

PUBLICATIONS

- **Cheeseman IH**, Miller BA, Nair S, Nkhoma S, Tan A, Tan JC, Al Saai S, et al. A major genome region underlying artemisinin resistance in malaria. *Science* 2012; 336 (6077):79-82. PMID: 22491853
- **Cheeseman IH**, McDew-White M, Phyo AP, Sriprawat K, Nosten F, Anderson TJ. Pooled sequencing and rare variant association tests for identifying the determinants of emerging drug resistance in malaria parasites. *Mol Biol Evol* 2015; 32 (4):1080-90. PMID: 25534029
- Nair S, Nkhoma SC, Serre D, Zimmerman PA, Gorena K, Daniel BJ, Nosten F, Anderson TJ, **Cheeseman IH**. Single-cell genomics for dissection of complex malaria infections. *Genome Res* 2014; 24 (6):1028-38. PMID: 24812326

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/1x7nmfMEimzkB/bibliograpahy/44933402/public/?sort=date&direction=ascending

SHELLEY A. COLE, PH.D.

STAFF SCIENTIST III, GENETICS

RESEARCH FOCUS

Dr. Cole studies the genetic risk for developing common, complex diseases. She collaborates on genetic studies of minority population groups that have very high rates of metabolic and other diseases yet are traditionally under-represented in genetic and medical research.

- **Diseases:** Metabolic syndrome; heart disease, diabetes, obesity, hypertension, kidney disease
- Applying molecular genetic techniques for medium and high-throughput collection of genetic information
- Identifying novel genetic risk markers in understudied population groups

A special focus of Dr. Cole's work is on preserving and promoting the utility and potential of the Strong Heart Study as a national resource for research studies to ultimately reduce the prevalence and incidence of metabolic-related disease and to improve public health in general in the American Indian population. Dr. Cole has more than 25 years of expertise studying human genetics.

INSIDE THE LAB

We apply molecular genetic techniques for collection of genotypic, DNA sequencing, and gene expression data. These data are analyzed within the lab and through collaborations within the Department of Genetics and with investigators from other institutions across the United States.

Our collaborations on population-based studies focus on family-based designs and look at molecular genetic variation and how it affects inter-individual variation in disease risk and treatment, particularly heart disease, hypertension, type 2 diabetes, kidney disease, obesity and their metabolic risk factors and consequences. We focus on American Indians (the Strong Heart Study [SHS] with representatives from 13 U.S. tribes, the Zuni Indians [GKDZI]), Alaskan Eskimos (GOCADAN), Mexican Americans (*VIVA la Familia*) and African Americans (PATH). These underserved minority populations with increased prevalence of metabolic and complex diseases are understudied relative to populations of European descent, especially when looking at how genetic risk factors affect disease and are modified according to ancestral backgrounds and environmental risk factors. We mainly use a family-based study design with multigenerational pedigrees, providing rich datasets for identification of rare and population-specific genetic variants. My previous research and current lab have generated molecular genetic data using samples from these population groups. In some cases it is the first generation of such data for a particular population group.

The Strong Heart Study of American Indians (SHS) is one of the largest (>7,600 participants) and longest-running (since 1988) epidemiological and genetic studies of American Indians in the US. SHS showed that American Indians have some of the highest rates of type 2 diabetes and cardiovascular disease (CVD) relative to other population groups in the US, helped determine type 2 diabetes as a major risk factor for CVD, and has been used by the Indian Health Service to develop treatment guidelines. I have been part of the SHS for more than 15 years, currently as PI of the SHS Genetics Center (since 2008) and Chair of the SHS Steering Committee (since 2014), representing five SHS centers, including its tribal partners.

Impact of common and rare genetic variants on disease. Our goal is to characterize molecular genetic variation and how it affects inter-individual variation in disease risk and treatment. In a collaboration on childhood obesity in the VIVA la Familia cohort, we identified a novel loss-of-function mutation (G55V) in *MC4R* and confirmed that it was responsible for the severe obesity seen in six related children. We also showed associations between *MC4R* variants and obesity measures in the entire childhood cohort, demonstrating that variants in *MC4R* have impacts on both rare, severe obesity as well as population-level obesity traits. We conducted a sequencing analysis of the *FVIII* gene in Black hemophilia patients as part of a study on inhibitor development to factor VIII (FVIII) replacement therapy in patients with hemophilia. It showed sequence variants present in Black patients that aren't represented in the therapeutic replacement FVIII protein, which may affect inhibitor development and, if confirmed, indicates that therapies must consider the potential genetic differences present between population groups.

MAIN TECHNOLOGIES AND METHODS USED

- High-and medium-throughout genotyping
- Illumina DNA sequencing
- Gene expression analysis
- Family study design

PUBLICATIONS

- **Cole SA**, Butte NF, Voruganti VS, Cai G, Haack K, Kent JW Jr, Blangero J, Comuzzie AG, McPherson JD, Gibbs RA. Evidence that multiple genetic variants of MC4R play a functional role in the regulation of energy expenditure and appetite in Hispanic children. *Am J Clin Nutr* 2010 Jan;91(1):191-9. PMID: 19889825 PMC2793108

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/shelley.cole.1/bibliography/40101172/public/?sort=date&direction=ascending

ANTHONY G. COMUZZIE, PH.D.

SCIENTIST, GENETICS

RESEARCH FOCUS

Dr. Comuzzie is an expert on the genetics of cardiometabolic diseases. He investigates the complex picture of how genetics and diet interact to influence a wide array of medical conditions, including obesity, diabetes, heart disease, brain functioning, and prenatal development. For this, he works with large family-based cohorts and non-human primate models. He made significant contributions to the genetic epidemiology of cardiometabolic diseases (risk for diabetes, heart disease or stroke and related pathologies).

- **Diseases:** cardiovascular disease, obesity, diabetes
- Ethnic population studies
- Nonhuman primate studies

Dr. Comuzzie has more than 20 years of experience in genetic epidemiology and the genetics of complex metabolic traits. He has been working with the baboon as a model for the study of obesity, diabetes, and heart disease for more than 15 years.

INSIDE THE LAB

All of our studies utilize large, family-based cohorts to identify the genetic contribution to cardiometabolic conditions. Our lab conducts numerous studies in a variety of ethnic populations that include Mexican Americans (both adults and children), Native Americans, Alaskan Eskimos, and Omani Arabs.

Nonhuman primate models. I have lead efforts to develop the baboon as an experimental model for research in cardiometabolic diseases, and my lab is currently involved in the development and application of this unique nonhuman primate resource in translational applications. As part of this work with baboons I have directed the development of a high fat/high carbohydrate challenge diet which showed pronounced and rapid negative effects on a range of key metabolic parameters, consistent with the metabolic disruptions seen in humans. Our pilot studies with baboons demonstrated how a combination of fat and sugar accelerated the development of obesity and metabolic dysfunction in this research model for human atherosclerosis and diabetes. This finding resulted in numerous collaborations with researchers around the world who are now adapting this diet for use with other nonhuman primate models in the study of prenatal development, diabetes, cardiovascular disease and cancer risk.

In addition, we have successfully implemented several key procedures in our baboon model, including the euglycemic clamp protocol, a method for quantifying insulin secretion and resistance.

Ethnic population studies. The genetic aspects of energy expenditure are not well studied because few facilities have the capability to collect that type of data and analyze it in large numbers of people, certainly not in a family study situation.

Our state-of-the-art equipment at Texas Biomed offers unparalleled resources for investigating heritable factors that influence obesity and comorbidities. We have generated over a million SNP typings and a genome-wide association study, and are analyzing calorimetry data from 1,400 participants in the Viva La Familia study. This study is generating information about novel genes that influence the energy expenditure rates in cells.

Our group uncovered new information about the melanocortin 4 receptor gene previously linked to rare, but heritable cases of extreme obesity. We have identified other variants of the same gene that are more common and that cause more moderate effects in a greater number of people.

My lab also works on the evolution of skin pigmentation in Indigenous-American populations, under the direction and leadership of Dr. Ellen Quillen.

Our Oman Family Study research program looks at the role of genetic and environmental factors in complex diseases (hypertension, diabetes, obesity, the metabolic syndrome) and concentrates on developing and evaluating clinical interventions to address health care needs. This collaboration includes basic and clinical sciences in Sultan Qaboos University, Ministry of Health, and international institutions of similar research interests.

MAIN TECHNOLOGIES AND METHODS USED

- High-throughput phenotyping (Luminex, Immulite)
- Statistical genetics methods
- Dietary manipulation
- Tether studies

PUBLICATIONS

- Mou Z, Hyde TM, Lipska BK, Martinowich K, Wei P, Ong CJ, Hunter LA, Palaguachi GI, Morgun E, Teng R, Lai C, Condarco TA, Demidowich AP, Krause AJ, Marshall LJ, Haack K, Voruganti VS, Cole SA, Butte NF, **Comuzzie AG**, Nalls MA, Zonderman AB, Singleton AB, Evans MK, Martin B, Maudsley S, Tsao JW, Kleinman JE, Yanovski JA, Han JC. Human obesity associated with an intronic snp in the brain-derived neurotrophic factor locus. *Cell Rep* 2015 Nov 10;13(6):1073-80. PMID: 26526993, PMC4644471
- Butte NF, Liu Y, Zakeri IF, Mohney RP, Mehta N, Voruganti VS, Göring H, Cole SA, **Comuzzie AG**. Global metabolomic profiling targeting childhood obesity in the Hispanic population. *Am J Clin Nutr* 2015 Aug;102(2):256-67. PMID: 26085512, PMC4515872
- Laston SL, Voruganti VS, Haack K, Shah VO, Bobelu A, Bobelu J, Ghahate D, Harford AM, Paine SS, Tentori F, Cole SA, MacCluer JW, **Comuzzie AG**, Zager PG. Genetics of kidney disease and related cardiometabolic phenotypes in Zuni Indians: the Zuni Kidney Project. *Front Genet* 2015 Jan 30;6:6. doi: 10.3389/fgene.2015.00006. eCollection 2015. PMID: 25688259, PMC4311707

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/anthony.comuzzie.1/bibliography/47845297/public/?sort=date&direction=ascending

LAURA A. COX, PH.D.

SCIENTIST AND VICE CHAIR, GENETICS; LEADER, EXPERIMENTAL PHYSIOLOGY & GENOMICS UNIT, SNPRC

RESEARCH FOCUS

Dr. Cox works mainly on the identification and characterization of genes involved with development of cardiovascular disease. For that, the Cox lab develops genetic and genomic tools and methods for Non Human Primate (NHP) research, including large-scale baboon studies in the pedigreed, phenotyped colony at SNPRC. These essential tools for molecular genetic and genomic studies in baboon allow studies of cardiovascular and other complex diseases.

Dr. Cox also genetically manages the colony of the Indian-origin specific pathogen free (SPF) rhesus monkeys for AIDS-related research.

- Development of NHP genetic and genomic resources
  a. Pedigreed baboon genome for biomedical research
- Genetic variation that influences risk of cardiovascular disease
  a. Network responses to dietary fat in individuals with good cholesterol profiles versus bad cholesterol profiles
  b. Gene variants and mechanisms of salt-sensitive hypertension
- Genetic and epigenetic responses to the maternal environment
  a. Maternal environment (*in utero*) influence on adult risk of heart disease. Potential therapeutic targets for modulation of blood pressure and serum cholesterol

Dr. Cox has more than 30 years of experience working in the area of genetics.

INSIDE THE LAB

NHP Genetic and Genomic Resources: Pedigreed Baboon Genome Resource for Biomedical Research. Baboons have been studied for >50 years and are ideal model organisms to study complex human diseases such as hypertension, atherosclerosis, diabetes, and osteoporosis. Our studies are performed on samples from phenotyped, genotyped, pedigreed baboons, allowing targeted selection of discordant animals to analyze complex genetic traits.

We constructed a baboon genetic linkage map that is the foundation of genetic variant localization for quantitative traits. In collaboration with Dr. Jeff Wall (UCSF), our lab is sequencing 700 baboon genomes from the pedigreed colony. We also created an analysis pipeline using an iterative approach with multiple reference genomes to annotate genome sequences for species without an existing high quality reference genome, or with a poorly annotated reference genome.

Genetic variation that influences risk of cardiovascular disease. Combining animal selection with molecular genetic and genomic approaches, our lab identified a gene splice variant that directly impacts LDL cholesterol serum concentrations; the same class of splice variant was later identified in humans. We expanded this approach from single gene analyses to integrated gene/microRNA network analyses, resulting in the identification of a network of candidate genes and microRNAs that underlie variation in serum LDL cholesterol concentrations.

Discovery of gene variants and mechanisms underlying salt-sensitive hypertension. Our lab works on identifying genetic polymorphisms and networks that underlie variation in blood pressure response to dietary sodium in baboons.

Establishment of a SPF rhesus macaque colony, MHC typing and genetic characterization core. We genetically manage the colony of the Indian-origin specific pathogen free (SPF) rhesus monkeys for AIDS-related research at SNPRC and are in the process of genetically characterizing the colony by genotyping 219 animals per year using the novel genotyping-by-sequencing (GBS) method.

Genetic and epigenetic responses to the maternal environment. In collaboration with Dr. Peter Nathanielsz, we study how the maternal environment influences offspring risk of developing heart disease. Our goal is to identify genetic networks and gene variants that provide potential therapeutic targets for modulation of blood pressure and serum cholesterol.

Novel mouse model of obesity in pregnancy. For characterizing a new mouse model of obesity in pregnancy and its links to the development of metabolic syndrome in the offspring, we perform RNA-Seq and small RNA-Seq of fetal tissue samples, placental tissue samples and post-natal offspring in collaboration with UC Denver.

MAIN TECHNOLOGIES AND METHODS USED

- Illumina DNA-Seq
- Illumina RNA-Seq and small RNA-Seq
- NGS assembly and annotation pipeline for non-human genomes
- SNP genotyping
- Genotyping-by-sequencing
- Bioinformatic analyses of genomic and transcriptomic data
- Comparative genomics
- QRT-PCR
- Western blots

PUBLICATIONS

- Karere GM, Glenn JP, Birnbaum S, Rainwater DL, Mahaney MC, VanderBerg JL, **Cox LA**. Identification of candidate genes encoding an LDL-C QTL in baboons. *J Lipid Res* 2013; 54:1776-1785. PMC3679381
- Pereira SP, Oliveira PJ, Tavares LC, Moreno AJ, **Cox LA**, Nathanielsz PW, Nijland MJ. Effects of moderate global maternal nutrient reduction on fetal baboon renal mitochondrial gene expression at 0.9 gestation. *Am J Physiol Renal Physiol* 2015. PMID: 25761880, PMC4587598

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/42185600/?u=202

MARCEL DAADI, PH.D.

ASSOCIATE SCIENTIST; LEADER, REGENERATIVE MEDICINE AND AGING UNIT, SNPRC

RESEARCH FOCUS

Dr. Daadi is an expert in regulated translational research and has developed therapeutic neural stem cell lines (NSC) for clinical use in Parkinson's disease, stroke, and to target brain tumors in both industrial and academic settings. He discovered a novel technique of engineering these stem cell lines from pluripotent human embryonic stem cells and continues to develop this therapeutic cell line for clinical use.

Dr. Daadi came to Texas Biomed in 2014 and is the team leader for the SNPRC Regenerative Medicine and Aging research unit. Results from his studies are the foundation of translational research and help to repair diseased or injured brain through transplantation of highly purified NSCs and stimulation of internal repair mechanisms.

Dr. Daadi's current focus is on:

- Parkinson's disease, Stroke, Traumatic Brain Injury (TBI), Multiple Sclerosis (MS)
- Human neural stem cells (NSCs)
- Non human primate studies

Previously, Dr. Daadi worked as Senior Scientist and group leader to start the NSC program at Layton Biosciences, the world's first biotech company to develop and manufacture a neural product to treat stroke patients. While at Stanford University, he started a human embryonic stem cell program to develop therapeutic cell lines for treating Parkinson's disease and stroke. He has more than 20 years of expertise in stem cell research..

INSIDE THE LAB

My research interests span both basic biology and translational research. We are pursuing reprogramming and genome-editing technologies to model neurological disorders *in vitro* and to understand mechanisms mediating disease development and degenerative processes following injury or disease.

Our group is currently focused on developing technologies to establish pluripotent stem cells, isolate self-renewable multipotent NSCs and generate specific neuronal lineages, such as dopaminergic neurons for treating Parkinson's disease. We explore the cellular and molecular mechanisms underlying the generation and differentiation of multipotent human NSCs from human pluripotent stem cells.

Our lab is currently testing the safety and efficacy of therapeutic cell lines through use of relevant neurological disease animal models by applying cell delivery and multimodal molecular imaging techniques.

As part of the SNPRC, we are also focused on preclinical development using a non-human primate model of Parkinson's disease, stroke, MS and TBI. We are genetically engineering NSCs to investigate the role of optogenetics on their fate after grafting. These studies will help determine the mechanisms mediating stem cell graft–host interactions in enhancing neuro-regeneration and restoring function.

MAIN TECHNOLOGIES AND METHODS USED

- Stem cell isolation, cloning, perpetuation and differentiation
- Induced pluripotent stem cells-based disease modeling
- Neural stem cell manufacturing
- Neurophysiological recording
- Animal models of neurological disorders
- MRI-based neurosurgical interventions
- Multimodal molecular imaging

PUBLICATIONS

- Azevedo-Pereira RL, **Daadi MM**. Isolation and purification of self-renewable human neural stem cells for cell therapy in experimental model of ischemic stroke. *Methods in Mol Biol* (Clifton, N.J.). 2013, 1059:157-67. PMID: 23934842
- **Daadi MM**, Grueter BA, Malenka RC, Redmond DE Jr, Steinberg GK. Dopaminergic neurons from midbrain-specified human embryonic stem cell-derived neural stem cells engrafted in a monkey model of Parkinson's disease. *PloS One* 2012, 7(7):e41120. PMID: 22815935, PMC3398927
- **Daadi MM**, Barberi T, Shi Q, Lanford RE. Nonhuman primate models in translational regenerative medicine. *Stem Cells Dev* 2014, 23 Suppl 1:83-7. PMID: 25457970, PMC4236035

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/41952413/

ROBERT DAVEY, PH.D.

DEPARTMENT CHAIR AND SCIENTIST, VIROLOGY AND IMMUNOLOGY, EWING HALSELL SCHOLAR

RESEARCH FOCUS

Dr. Davey is interested in understanding how viruses like Ebola virus penetrate the cell membrane and establish infection. In addition, the Davey laboratory has developed safe, efficient, high-throughput screening techniques for Ebola virus and performs contract work on testing drugs and compounds against Ebola virus infection in the BSL-4 maximum containment laboratory. This work has resulted in exciting findings towards potential drug candidates to combat Ebola virus. Dr. Davey has been working with:

- Filoviruses: Ebola virus, Marburg virus
- Lassa fever virus
- Bunyaviruses: Crimean-Congo hemorrhagic fever virus

Dr. Davey contributes more than 25 years of expertise in virology and has been studying Ebola virus since 2006; his recent work has been published in high-impact journals that include *PLoS Pathogens*, *PNAS* and a cover feature in *Science*.

INSIDE THE LAB

Drug screening. Ebola virus outbreaks, such as the 2014 epidemic in West Africa, are episodic and deadly, and filovirus antivirals are currently not clinically available. With our team well trained in ABSL-4 procedures, our lab performs contract work on testing drugs and compounds for the inhibition of Ebola virus infection; we also collaborate with several groups on the study of pathogenic viruses, with a main focus on Ebola virus. Our lab applies sophisticated molecular and cell biology techniques, including high throughput screening techniques for Ebola viruses. Using industry standard 384-well plates, we can screen thousands of small molecules for those that have potential as therapies. Combined with customized computer software to automatically identify infected cells and determine drug efficacy, our semi-automated approach drastically reduces the time to find effective drugs by 90% over traditional methods.

Our lab is using this platform to perform drug testing for NIH, private drug companies as well as academic scientists. The hits from this work are then analyzed for how they work. Using this approach, tetrandrine is showing promise for use against Ebola virus and genistein appears broadly active against Lassa fever virus as well as Ebola virus.

Cellular factors important for establishing infection. Another aspect of our research is the identification of cellular factors important for establishing infection by filoviruses and bunyaviruses. Our studies have allowed a deeper understanding of the entry and cell signaling pathways used by each virus to penetrate the cell membrane and establish infection. We were the first to demonstrate that PI3 kinase is a trigger for Ebola virus uptake and that macropinocytosis is the major pathway for productive infection. Most recently, we demonstrated that Ebola virus entry into host cells requires the endosomal calcium channels called two-pore channels (TPCs), and that TPC proteins play a key role in Ebola virus infection and may constitute effective targets for antiviral therapy. Similarly, we were the first to show that Crimean Congo virus uses specialized sorting organelles called multivesicular bodies to enter into the cell cytoplasm; blocking access to these organelles prevents infection.

Treatment options. We found that the FDA-approved drug interferon gamma may serve as a novel and effective prophylactic or treatment option. Using mouse-adapted Ebola virus, we found that giving the innate immune response a kick-start using interferon gamma, animals were protected from disease and reduced morbidity and serum virus titers. We think this works by priming macrophages so that they more aggressively attack virus-infected cells and making themselves inherently resistant to infection.

Immunodiagnostics. The ongoing evolution of Ebola viruses poses significant challenges to the development of immunodiagnostics for detecting emergent viral variants, showing a critical need for the discovery of monoclonal antibodies with distinct affinities and specificities for different Ebola viruses. We developed an efficient technology for the rapid discovery of antigen-specific monoclonal antibodies from immunized animals by mining the VH:VL paired antibody repertoire encoded by highly expanded B cells in the draining popliteal lymph node (PLN). This approach requires neither screening nor selection for antigen-binding. This collaborative effort with UT Austin scientists will aid in development of better vaccines and is also currently being developed as a potential new rapid diagnostic platform.

MAIN TECHNOLOGIES AND METHODS USED

- High throughput screening techniques
- Cell biology techniques including microscopy and siRNA suppression of gene expression
- Computer assisted image analysis
- Efficacy of treatments by *in vitro* and *in vivo* disease models

PUBLICATIONS

- Sakurai Y, Kolokoltsov AA, Chen CC, Tidwell MW, Bauta WE, Klugbauer N, Grimm C, Wahl-Scott C, Biel M, **Davey RA**. Ebola virus. Two-pore channels control Ebola virus host cell entry and are drug targets for disease treatment. *Science*. 2015 347(6225):995-8. PMID 25722412, PMC4550587
- Rhein BA, Powers LS, Rogers K, Anantpadma M, Singh BK, Sakurai Y, Bair T, Miller-Hunt C, Sinn P, **Davey RA**, Monick MM, Maury W. Interferon-γ Inhibits Ebola Virus Infection. *PLoS Pathog* 2015 Nov 12;11(11):e1005263. doi: 10.1371/ journal.ppat.1005263. eCollection 2015 Nov. PMID: 26562011, PMC4643030

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/robert.davey.1/bibliography/48523036/public/?sort=date&direction=ascending

MELISSA DE LA GARZA, M.S., D.V.M.

ASSOCIATE VETERINARIAN, SNPRC

RESEARCH FOCUS

Dr. de la Garza, a laboratory animal medicine veterinarian, has more than 10 years of experience working with non human primates (NHP).

A major responsibility of a lab animal veterinarian is to maintain healthy colonies using preventative medicine and to investigate ways to better treat common, chronic, or progressive diseases. Dr. de la Garza's primary responsibilities include:

- Daily health care monitoring of the aging chimpanzee colony
- Veterinary support to research protocols involving NHPs and other lab animals
- Supporting other animal colonies housed at Texas Biomed

CHIMPANZEES

Dr. de la Garza is the primary clinician for the chimpanzee colony. Chimpanzees are not currently used in research; however, they are a long-lived species exhibiting disease states and courses that closely mirror those of humans. Thus their routine monitoring and preventive care is comprehensive, multifaceted and must be provided for life.

In order to reduce boredom and anxiety, these highly intelligent animals are housed in large and complex facilities. The caretakers are encouraged to develop relationships with each animal and get acquainted with their individual likes and dislikes and unique characteristics. All animals benefit from an in-house, highly skilled veterinary support staff as well as the expertise of colleagues from the world of human medicine.

Dr. de la Garza spends a great deal of her time seeing to the clinical needs of a chimpanzee colony that is quickly becoming geriatric. During her 10 years as primary veterinarian providing clinical care for this chimp colony, she has developed bonds and meaningful relationships with most of the animals in the colony. Her work involves providing preventative care in the form of their annual physical exams as well as responding to illness, trauma and emergencies that arise throughout the year. Conducting a physical exam on one chimp takes a considerable amount of time, and maintaining the health of large chimp colony at SNPRC requires continuous clinical oversight. As the chimp colony ages, more animals develop chronic, progressive, or age-related illness that must be managed. Because cardiac disease is a leading cause of death in captive chimps, her efforts concentrate on heart health. Since dental disease has been linked to cardiac health, Dr. de la Garza also places a great emphasis on dental care. Because the chimpanzee is a highly advanced animal with complicated environmental needs, she works with the Behavioral Services and care team to help provide for their behavioral needs, paying special attention to the personalities and social histories so that they may be housed with compatible individuals.

RESEARCH SUPPORT

In the past, Dr. de la Garza and her colleagues have acquired the expertise to work with multiple hemorrhagic fever viruses (e.g. Ebola, Marburg, Lassa), multidrug resistant bacteria, and various emerging pathogens in rodent, rabbit and non-human primate models. This included work in high containment facilities, ABSL-3 and ABSL-4.

Her group has been supporting a multitude of research projects in infectious disease, experimental surgery, cardiovascular disease, metabolism, pharmacokinetics, vaccine development, and behavior. A thorough review of study protocols, close monitoring of the animals, and continuous communication with investigators throughout the course of each study is essential to optimize research outcomes.

All of the clinical veterinarians work together to provide the best possible care for each of the various species and colonies. Dr. de la Garza works closely with Dr. Brasky to support the marmoset colony as well as rodent species that may be housed at Texas Biomed. She will also be called upon to provide support to the baboon and macaque colonies.

Dr. de la Garza is chairman of the San Antonio Area Foundation Biomedical Research Community Advisory Committee. She shares her knowledge and expertise through a variety of community outreach activities, including regular community teaching on non-human primate care biosafety.

Recently, Dr. de la Garza switched her focus to new studies. Her new collaborations include studies on *Streptococcus pneumoniae* and epilepsy baboons. She is also hoping to develop a program of conducting routine echocardiogram examinations on chimpanzees as well as other nonhuman species that are prone to cardiac disease.

PUBLICATIONS

- Szabo C, **de la Garza M**, Rice K, Bazan C, Salinas F. Colpocephaly in a Baboon Pedigree: relationship to the Epileptic Phenotype. *Comparative Medicine*, in press
- Cepeda M, Salas M, Folwarczny J, Leandro AC, Hodara VL, **de la Garza MA**, Dick EJ Jr, Owston M, Armitige LY, Gauduin MC. Establishment of a neonatal rhesus macaque model to study Mycobacterium tuberculosis infection. (Edinb). 2013 Dec;93 Suppl:S51-9. doi: 10.1016/S1472-9792(13)70011-8. PMID: 24388650, PMC4051704
- **De la Garza, MA**. Thorax conditions. In: Pocket Handbook of Nonhuman Primate Clinical Medicine. Courtney, A., eds. Boca Raton, CRC Press. 2013: 103-116

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47848252/?sort=date&direction=ascending

EDWARD DICK, JR., D.V.M.

VETERINARIAN/ PATHOLOGIST, SNPRC

RESEARCH FOCUS

Dr. Dick is a board-certified veterinary pathologist with more than 25 years of experience in biomedical research, laboratory animal medicine, and pathology. Pathology is not only a medical and diagnostic discipline, but also a scientific discipline that focuses on the examination of tissues to diagnose disease and studies the etiology and pathogenesis of disease. Dr. Dick evaluates pathologic changes in multiple species in both a diagnostic capacity and in a variety of research studies, specifically toxicity, infectious disease, diet, metabolism and obesity-related pathology.

He provides pathology support for:

- Monitoring the health of all Texas Biomed/SNPRC nonhuman primate colonies and other animals
- Studies of the pathogenesis and treatment of obesity, metabolic disease, and diabetes
- Identification and characterization of infectious diseases in non- human primates
- Studies of reproductive pathology and maternal-fetal interactions

His collaborations and support encompass the clinical care of the colonies and varied research programs at SNPRC that resulted in multiple publications.

One of Dr. Dick's primary goals is to better define the pathology of the various primate species and disseminate that information to the scientific community.

He has developed pathology reviews for many of the SNPRC-housed species and created a pathology study set for pathology, laboratory animal, and wildlife veterinary clinicians and residents.

Dr. Dick has been identifying and describing new animal models to help in the understanding of pathogenesis and treatment of human and animal diseases.

MAIN TECHNOLOGIES AND METHODS USED

- Anatomic pathology
  - Necropsy
  - Histopathology
  - Immunohistochemistry
  - Stereological microscopy
- Clinical pathology
  - Clinical chemistry testing
  - Hematology testing
  - Coagulation testing
  - Parasitology
  - Microbiology

PUBLICATIONS

- **Dick EJ Jr**, Owston M, David JM, Sharp RM, Rouse S, Hubbard GB. Mortality in captive baboons (Papio spp.): a 23-year study. *J Med Primatol* 2014 Jun; 43:169-196. NIHMS553896, PMC3989440
- Guardado-Mendoza R, Perego C, Finzi G, Larosa S, Capella C, Jimenez-Ceja LM, Velloso LA, Saad JA, Sessa F, Bertuzzi F, Moretti A, **Dick EJ Jr**, Davalli AM, Folli F. Delta cell death in the islets of Langerhans and the progression from normal glucose tolerance to type 2 diabetes mellitus in non-human primates (Baboons, *Papio hamadryas*). *Diabetologia* 2015, 58(8):1814-26. 2015. PMID: 26049399
- Whatmore AM, Davison N, Cloeckaert A, Al Dahouk S, Zygmunt MS, Brew SD, Perrett LL, Koylass MS, Vergnaud G, Quance C, Scholz HC, **Dick EJ Jr**, Hubbard G, Schlabritz-Loutsevitch NE. Brucella papionis sp. nov. isolated from baboons (*Papio* spp.). *Int. J. Syst. Evol Microbiol* 2014, 64(Pt 12):4120-8. PMID: 25242540
- David JM, **Dick EJ Jr**, Hubbard GB. Spontaneous pathology of the common marmoset (*Callithrix jacchus)* and tamarins *(Saguinus oedipus, Saguinus mystax*). *J Med Primatol* 2009 Oct; 38:347-359. NIHMS129363, PMC2740810

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47808480/?sort=date&direction=ascending

PATRICE FROST, D.V.M.

VETERINARIAN, SNPRC

RESEARCH FOCUS

Dr. Frost has been employed at major primate research facilities for more than 30 years. She has managed breeding colonies and conducted clinical, surgical support and experimental procedure development involving marmosets, tamarins, owl monkeys, baboons, chimpanzees, and multiple macaque species.

As a senior veterinarian, she provides support to the SNPRC for its clinical and research programs. In this role, she has developed and instituted a baboon breeding program and research protocols to support the study of fetal programing and stem cells. Dr. Frost has managed macaque breeding programs at several facilities in various configurations from time-mated pairs to large group enclosures. In addition to extensive experience in breeding and health management of macaques, she has extensive experience in transferring entire populations of non-human primates (macaques and chimpanzees) between institutions. She was instrumental in the planning of the transfer and re-socialization of three entire populations of macaques (600 rhesus and 1,500 cynomolgus) to our existing facility.

Currently, Dr. Frost has daily oversight of the scheduling and the performance of the breeding and health needs of macaques, including routine health exams, selection of breeder replacements, reproductive soundness of both males and females, pregnancy management, post-partum evaluation, surgical intervention when necessary, and infant reintroduction.

Her diverse background and experience in the field of laboratory medicine has provided her with the opportunities to work in multiple research areas, ranging from vaccine development to Good Laboratory Practice (GLP) projects and model development.

Her most recent collaborative research efforts at SNPRC include the development of an obesity model in baboon and metabolic profiling and experimental production of a diabetic model using streptozotocin (STZ).

PUBLICATIONS

- **Frost PA**, Chen S, Mezzles MJ, Voruganti VS, Nava-Gonzalez EJ, Arriaga-Cazares HE, Freed KA, Comuzzie AG, DeFronzo RA, Kent JW Jr, Grayburn PA, Bastarrachea RA. Successful pharmaceutical-grade streptozotocin (STZ)-induced hyperglycemia in a conscious tethered baboon *(Papio hamadryas)* model. *J Med Primatol* 2015 Aug;44(4):202-17. doi: 10.1111/jmp.12182. Epub 2015 Jun 30. PMID: 26122701
- Bauer C, **Frost PA**, Kirschner S. Pharmacokinetics of 3 Formulations of Meloxicam in Cynomolgus Macaques *(Macaca fascicularis). J Am Assoc Lab Anim Sci* 2014, Sep; 53(5): 502–511.PMID: 2525507, PMC4181692
- Chen S, Bastarrachea RA, Roberts BJ, Voruganti VS, **Frost PA**, Nava-Gonzalez EJ, Arriaga-Cazares HE, Chen J, Huang P, DeFronzo RA, Comuzzie AG, Grayburn PA. Successful β cells islet regeneration in streptozotocin-induced diabetic baboons using ultrasound-targeted microbubble gene therapy with cyclinD2/CDK4/GLP1. *Cell Cycle* 2014, 13(7):1145-51. doi: 10.4161/cc.27997. Epub 2014 Feb 10. PMID:24553120, PMC4013164

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47895081/?sort=&direction=

MARIE-CLAIRE GAUDUIN, PH.D.

ASSOCIATE SCIENTIST, VIROLOGY AND IMMUNOLOGY, SNPRC

RESEARCH FOCUS

Dr. Gauduin has more than 25 years of experience in HIV/AIDS research and medical microbiology. She has been working extensively on HIV and the development of novel vaccine strategies using the non-human primate model for AIDS. In her work, she uses epithelial stem cells and weakened recombinant papillomavirus as vaccine-vectors to protect against multiple low-dose mucosal challenges. Dr. Gauduin is also developing a neonatal model for tuberculosis to study HIV/TB co-infection in pediatric AIDS.

Her specific research interests are:

- Early events of simian immunodeficiency virus (SIV) transmission in a macaque model
- Host immune responses to infectious diseases
- Early virus-specific T cell responses in neonates
- Tuberculosis/SIV coinfection in pediatric AIDS

INSIDE THE LAB

SIV transmission. Our lab is investigating the early events of SIV transmission in macaques using a recombinant SIV tagged with a green fluorescent protein (GFP) as a sensitive tool to monitor infected cells *in vivo*. This construct allows us to identify the:

1) initial infected cells, their phenotype and function
2) mechanisms, time course, and routes of viral spread from the site of initial infection to lymphoid organs and blood
3) generation of early SIV-specific immune response from the mucosal site of infection

These factors are critical for the development of effective vaccines.

HIV vaccine design and development. One key obstacle to an effective AIDS vaccine has been the inability to deliver antigen for a sufficient period of time. Because HIV transmission occurs mainly across mucosal surfaces, the ideal vaccine strategy would be to target HIV at mucosal entry sites of transmission to prevent infection. Our lab developed a novel vaccine strategy based on gene therapy with the goal to elicit a long-term immunity against HIV infection at the entry site of the virus. This strategy is based on the ability of therapeutic lentiviral vectors integrated in epidermal or mucosal epithelial stem cells to induce virus-specific cellular immune responses at mucosal sites against HIV/SIV. It represents an alternative approach using epithelial stem cells as a permanent source of viral antigen and their differentiated offspring as antigen-producing presenting cells.

Maternal transmission of HIV-1 accounts for most cases of pediatric HIV-1 infection. Using a macaque model, we are investigating the early virus-specific T cell responses in neonates orally infected with a pathogenic or non-pathogenic strain of SIV, (an HIV laboratory surrogate). We have shown that newborn monkeys infected with a less pathogenic SIV can control infection even in the absence of antiviral treatment, which suggests that treatment may be quite successful in "rescuing" or preserving the infant's immune response. Our present emphasis is on defining the mechanisms involved in oral SIV transmission to develop effective strategies to successfully block SIV transmission.

Tuberculosis (TB) is the leading cause of death among people with HIV, and pregnant women living with active TB and HIV are at greatest risk. Our group established an acute *Mycobacterium tuberculosis* infection in the newborn macaque model, optimized techniques to study acute pediatric TB infection in young macaques, and successfully demonstrated that it clinically and pathologically mimics the disease as seen in human infants. We confirmed that newborn macaques are highly susceptible to TB infection and can serve as a suitable animal model to study latent TB.

Our goal is the optimization of this model for TB/HIV co-infection to study immunopathogenesis of TB/SIV interactions and the impact of treatment and treatment interruption on the evolution of tuberculosis.

The development of an effective vaccine that restricts viral replication at the mucosal portal of entry may be our best hope for controlling HIV infection. Our experiments further refine the rationale for using vector vaccine strategies in advancing our understanding of the role of mucosal immune responses in protection, an area of considerable importance for AIDS vaccine research.

MAIN TECHNOLOGIES AND METHODS USED

- Vector-vaccine designs and development
- Cutting-edge quantitative virologic assays
- Polyfunctional intracellular staining techniques
- Humoral/cellular mucosal immune responses
- Vaccine efficacy and correlates of protection
- Non-human primate models for AIDS and TB

PUBLICATIONS

- Cepeda M, Salas M, Folwarczny J, Leandro AC, Hodara LV, de la Garza M, Dick E., M. Owston M, Hodora V, Armitige LY, **Gauduin MC**. Establishment of a neonatal macaque model to study pediatric *Mycobacterium tuberculosis* infection. *Tuberculosis* (Edinb). 2013, Dec;93 Suppl:S51-9. doi: 10.1016/S1472-9792(13)70011-8. PMID: 24388650, PMC4051704
- White R, Chenciner N, Bonello G, Salas M, Blancou P, **Gauduin MC**. Epithelial stem cells as mucosal antigen-delivering cells: A novel AIDS vaccine approach. *Vaccine* 2013, Nov 25. pii: S0264-410X(13)01233-4. doi: 10.1016/ j.vaccine.2013.09.006. PMID: 24286835, PMC4032815

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/marie-claire.gauduin.1/bibliography/47618018/public/?sort=date&direction= descending

LUIS GIAVEDONI, PH.D.

SCIENTIST AND VICE CHAIR, VIROLOGY AND IMMUNOLOGY, SNPRC

RESEARCH FOCUS

Dr. Giavedoni focuses his research on viral infections and the development of vaccines and therapies. He is particularly interested in understanding the immune responses to retroviral infections (e.g. HIV) in animal models. His lab works on cytokines, which are molecules that mediate communication between the immune system and the whole organism. His group has been developing technology for the identification of cytokines in nonhuman primates and also studies the potential use of cytokines.

- AIDS vaccine development using the rhesus macaque/simian immunodeficiency virus (SIV) model
- AIDS cure using CRISPR/Cas system and nanoparticle technology

Dr. Giavedoni is the leader of the Immunology Core Laboratory at SNPRC. He contributes more than 25 years of expertise in virology and more than 20 years of experience working with nonhuman primates; his scientific contributions led to an increase in the safety of vaccines.

INSIDE THE LAB

Non-human primates (NHP) present the most translational animal model available, due to their genetic and physiological similarities with humans. My laboratory has developed techniques for the identification of NHP cytokines using the Luminex technology, for the measurement of activation/proliferation markers and for the identification and isolation of cell subsets by flow cytometry. The resulting new methodologies have been made available to the entire scientific community.

More recently, I have been involved in work that utilizes select agents, and I am receiving training for performing future work in the ABSL-3 and ABSL-4 environments.

AIDS vaccine development in our lab is based on the rhesus macaque/simian immunodeficiency virus (SIV) model. Using this model in the field of AIDS pathogenesis, my laboratory was one of the first to identify the active role of NK cells during the acute phase of infection, and to demonstrate the utility of a low-stress tether system for frequent blood collection from unsedated macaques.

One of our collaborations is on the application of nanoparticle technology to deliver SIV genetic material to mucosal surfaces of macaques. This vaccination primed the immune system so that animals reacted with stronger immune responses when boosted with a second vaccine of a viral vector expressing the same genetic material. When exposed to an infectious SIV, half of the macaques resisted infection, an encouraging finding currently repeated in a larger and more controlled study.

A different AIDS-related project in our lab also involves nanoparticle technology, but here the particles carry small nucleic acids designed to bind and inactivate the viral genome within infected cells. We have identified four different molecules that can inhibit SIV replication and would reduce the chances for viral escape. We also identified five sets of guiding RNAs in the CRISPR/Cas system that can completely eliminate production of infectious virus.

Our work towards the creation of novel vaccines is based on chimeric proteins that can simultaneously induce and stimulate an immune response. These chimeric proteins are composed of one of the SIV glycoproteins which is then fused to a protein used by immune system cells to increase antibody production. Several of these chimeric proteins have been shown to have the capacity to stimulate macaque cells.

In collaboration with scientists in the Department of Genetics at Texas Biomed, our lab has been involved in identifying mechanisms that allow certain monkey species to resist natural infection with SIV; understanding these mechanisms may lead to new therapeutics treatments for HIV-infected individuals.

MAIN TECHNOLOGIES AND METHODS USED

- Nanoparticle technology
- Identification of cytokines with Luminex technology
- Measurement of activation/proliferation markers
- Flow cytometry
- ELISA
- ELISPOT

PUBLICATIONS

- Hao XP, Lucero CM, Turkbey B, Bernardo ML, Morcock DR, Deleage C, Trubey CM, Smedley J, Klatt NR, **Giavedoni LD**, Kristoff J, Xu A, Del Prete GQ, Keele BF, Rao SS, Alvord WG, Choyke PL, Lifson JD, Brenchley JM, Apetrei C, Pandrea I, Estes JD. Experimental colitis in SIV-uninfected rhesus macaques recapitulates important features of pathogenic SIV infection. *Nat Commun* 2015 Aug 18;6:8020. doi: 10.1038/ncomms9020. PMID: 26282376
- **Giavedoni LD**, Chen HL, Hodara VL, Chu L, Parodi LM, Smith LM, Sexton V, Cappelli D, Sodora DL. Impact of mucosal inflammation on oral simian immunodeficiency virus transmission. *J Virol* 2013,Feb;87(3):1750-8. doi: 10.1128/JVI.02079-12. Epub 2012 Nov 21. PMID: 23175379, PMC3554177
- Keckler MS, Hodara VL, Parodi LM, **Giavedoni LD**. Maintenance or emergence of chronic phase secondary cytotoxic T lymphocyte responses after loss of acute phase immunodominant responses does not protect SIV-infected rhesus macaques from disease progression. *J Biomed Biotechnol* 2010, 2010:279391. doi: 10.1155/2010/279391. Epub 2010 May 25. PMID: 20589067, PMC2877203

A complete list of publications can be found at
www.ncbi.nlm.nih.gov/myncbi/browse/collection/47853184/?u=202

ANTHONY GRIFFITHS

ASSOCIATE SCIENTIST, VIROLOGY AND IMMUNOLOGY,
ASSOCIATE DIRECTOR ABSL-4 LABORATORY

RESEARCH FOCUS

The Griffiths laboratory studies the biology of highly pathogenic viruses at high (Biosafety level 3, BSL-3) and maximum containment (BSL-4), under the umbrella of aiding the development of countermeasures. The need for countermeasures for these pathogens has been highlighted by the recent Ebola virus outbreak that originated in western Africa. Additionally, the agents we study are considered to have potential as bioterrorism agents, posing a threat to national security. The Griffiths lab studies the virus biology for the development of vaccines and therapeutics to prevent and treat infection.

- Ebola virus
- Marburg virus
- Sudan virus
- Venezuelan Equine Encephalitis virus
- Eastern Equine Encephalitis virus
- Western Equine Encephalitis virus

Dr. Griffiths has more than 20 years of expertise in virology with special focus on classical and molecular virology as tools to understand viral pathogenesis and zoonotic transmission.

INSIDE THE LAB

My lab is particularly interested in highly pathogenic viruses. This includes Ebola virus and Marburg virus that have high case fatality rates.

We study infectious forms of these RNA viruses in a BSL-4 maximum containment laboratory.

Typically, RNA viruses have high spontaneous mutation rates due to error-prone RNA-dependent RNA polymerases. Consequences of high spontaneous mutation and replication rates are populations composed of heterogeneous swarms of related variant sequences, sometimes called quasispecies. We are investigating the importance of this diversity to filovirus replication and pathogenesis *in vitro* and *in vivo*. Additionally, we are exploring the potential to exploit the high mutation rate as a therapeutic mechanism. Specifically, we work to understand the roles of the individual genotype populations in virus infection.

Many of our studies build on recent advances in sequencing and we use Illumina sequencing machines and a MiSeq in our laboratory. Our system permits quantification of the individual viral genotypes in a sample, and we have developed techniques to rapidly sequence whole viral genomes, including the 5' and 3' termini. Currently, we are expanding the use of our machines to gene expression and ribosome profiling of cells, and to tissues infected with BSL-4 pathogens.

Among other funding sources, we currently receive funding from the Medical Countermeasure Systems Joint Project Management Office, JPEO-CBD (MCS), to support the advanced development of filovirus vaccines under the Animal Rule.

MAIN TECHNOLOGIES AND METHODS USED

- Viral growth requirements and particle characterization
- Electron microscopy
- Quantification of individual viral genotypes within a sample
- Rapid sequencing techniques for whole viral genomes, including the 5' and 3' termini
- Ultra deep sequencing
- MiSeq and Illumina
- Gene expression and ribosome profiling of cells and tissues infected with BSL-4 pathogens
- Optimization and validation of plaque assays
- RT-qPCR assays
- Novel diagnostic technologies
- Determination of vaccine efficacy
- Novel diagnostic technologies
- Determination of vaccine efficacy

PUBLICATIONS

- Alfson K, Avena L, Beadles M, Menzie H, Patterson J, Carrion R, **Griffiths A**. Genetic changes at the glycoprotein editing site associated with serial passage of Sudan virus. *J Infect Dis* 2015, Oct 1;212 Suppl 2:S295-304. doi: 10.1093/ infdis/jiv216. Epub 2015 Apr 28. PMID:25920319
- Alfson KJ, Beadles MW, **Griffiths A**. A new approach to determining whole viral genomic sequences including termini using a single deep sequencing run. *J Virol Methods* 2014, 208 (1), 1-5. PMID:25075935
- Alfson KJ, Avena LE, Beadles MW, Staples H, Nunneley JW, Ticer A, Dick EJ Jr, Owston MA, Reed C, Patterson JL, Carrion R Jr, **Griffiths A**. Particle-to-PFU ratio of Ebola virus influences disease course and survival in cynomolgus macaques. *J Virol* 2015; 89(13):6773-81. PMID: 25903348, PMCID: PMC4468478 (selected for journal Spotlight)

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/anthony.griffiths.1/bibliography/41417299/public/?sort=date&direction=ascending

SHANNAN HALL-URSONE, D.V.M.

ASSISTANT VETERINARIAN, SNPRC

RESEARCH FOCUS

Dr. Hall-Ursone joined SNPRC in 2015. She is highly skilled in veterinary and surgical procedures, Good Laboratory Practices (GLP), and in supervising animal care. Dr. Hall-Ursone has been working as a veterinarian for the past 10 years and has experience in working with a variety of different species, including non human primates. Her effective communication and training skills allow her to successfully supervise teams while ensuring adherence to all safety and compliance programs. Dr. Hall-Ursone assists other investigators in scientific research projects and is developing her own research program.

Prior to joining SNPRC, Dr. Hall-Ursone worked with a team to develop a Good Laboratory Practices program from the ground up, which entailed writing Standard Operating Procedures (SOPs), overseeing all required documentation, and providing GLP-specific training and support. She provided advice to scientific investigators for the experimental design and procedure techniques for protocols to be submitted to the Institutional Animal Care and Use Committee (IACUC).

PUBLICATIONS

- Chappell MG, Koeller CA, **Hall SI**. Differences in postsurgical recovery of CF1 mice after intraperitoneal implantation of radiotelemetry devices through a midline or flank surgical approach. *J Am Assoc Lab Anim Sci* 2011 Mar;50(2):227-37. PMID: 21439217 PMC3061424
- Cisney ED, Fernandez S, **Hall SI**, Krietz GA, Ulrich RG. Examining the role of nasopharyngeal-associated lymphoreticular tissue (NALT) in mouse responses to vaccines. *J Vis Exp* 2012 Aug 1;(66):3960. doi: 10.3791/3960. PMID: 22871688 PMC3476754.
- Fernandez S, Cisney ED, **Hall SI**, Ulrich RG. Nasal immunity to staphylococcal toxic shock is controlled by the nasopharynx-associated lymphoid tissue. *Clin Vaccine Immunol* 2011 Apr;18(4):667-75. PMID: 21325486 PMC3122560

A complete list of publications can be found at www.ncbi.nlm.nih.gov/pubmed/?term=Hall+SI

ANDREW HAYHURST, PH.D.

ASSOCIATE SCIENTIST, VIROLOGY AND IMMUNOLOGY

RESEARCH FOCUS

The Hayhurst laboratory works on selected Tier 1 biothreat agents and develops novel antibody engineering approaches to find new routes to detect and inhibit pathogens. Using live agent selections, his team develops antibodies that can recognize native biothreat antigens in a highly specific and sensitive manner. These antibodies are rugged enough for transition to biosensors and field portable diagnostics to withstand very harsh conditions, (e.g. in resource-poor areas of the world with limited electricity and refrigeration).

His lab has developed llama single domain antibodies (sdAb) specific for Ebola virus and Marburg virus, two viruses that cause hemorrhagic fever and a very high mortality rate.

Dr. Hayhurst and his team also developed an assay to recognize all serotypes of the botulinum neurotoxin, one of the most poisonous substances currently known.

The redesign of the surfaces of microbes allows us to "educate" them to perform simple tasks of interest to therapeutic and nanotechnology communities and is a recent focus of the Hayhurst lab.

- Ebola virus
- Marburg virus
- Botulinum neurotoxins
- Novel cancer therapeutics
- Nanotechnology

Dr. Hayhurst contributes more than 20 years of experience in microbiology and antibody engineering.

INSIDE THE LAB

Many biothreat agents lack high quality antibodies that are essential for the development of immunoassays and help to facilitate molecular studies. To circumvent this problem, we established an antibody pipeline to rapidly select and screen sdAb specific for BSL-4 agents. Our group was the first to apply single-pot selection to a live BSL-4 agent and we developed a highly sensitive assay for Marburg virus within only three weeks. Using our single-pot methodology, we also developed assays for five Ebola virus species and serendipitously revealed a common antigenic attractant within the nucleoprotein for all single domain antibodies (sdAb).

One focus has been on accelerating antibody screening within a viral sandwich assay to formulate stop-gap diagnostic assays. Our novel process rapidly identifies pairs of affinity reagents, including sdAb, without the need for protein purification. The approach relies upon the temporal occlusion of *in-vivo* biotin by neutravidin to enable "captors" and "tracers" to be sourced from the same extract. The ease, speed, and cost-effectiveness of the technology ensure that affinity reagent pairing is very straightforward, requires no sophisticated equipment, and accelerates the discovery of high performance antibodies.

Our research emphasis is moving on from reagent development and into more basic science as we study the molecular basis for recognition of the viral antigens by our sdAb using X-ray crystallography, in collaboration with Drs. Alex Taylor and John Hart at the UTHSCSA crystallography core laboratory. We are applying this information to guide antibody engineering to close the gap between immunoassay and nucleic acid based detection; our new strategies should be applicable to several RNA viruses to help safeguard human health.

Botulism, a muscle-paralyzing and potentially fatal disease, is caused by neurotoxins produced by the bacterium *Clostridium botulinum*. Using immune llama antibodies, our lab has been targeting the botulinum neurotoxins, estimated to be 100 billion times more toxic than cyanide. We have successfully engineered a heptaplex assay to recognize the seven known serotypes of the neurotoxin based upon sdAb, all of which have proved to be suitable for making multiplex biosensor platforms more rugged.

Our lab is also exploring the potential for reprogramming the surfaces of bacteria and viruses to enable them to more effectively target tumors. We are currently examining the limits of microbial cell surface display in terms of payload and degree of access to target antigens on mammalian target cells in contrast to typical solution phase antigens and substrates.

MAIN TECHNOLOGIES AND METHODS USED

- Recombinant antibody generation
- Phage display of peptides and proteins
- Rapid antibody pairing
- Protein engineering
- Directed evolution
- Protein production and purification
- Immunoassay development
- Novel therapeutic development

PUBLICATIONS

- Sherwood LJ, **Hayhurst A**. Ebolavirus nucleoprotein C-termini potently attract single domain antibodies enabling monoclonal affinity reagent sandwich assay (MARSA) formulation. *PLoS One* 2013, 8(4):e61232. doi: 10.1371/journal.pone.0061232. Epub 2013 Apr 5. PMID: 23577211, PMC3618483
- Sherwood LJ, **Hayhurst A**. Hapten mediated display and pairing of recombinant antibodies accelerates assay assembly for biothreat countermeasures. *Sci Rep* 2012, 2:807. PMID:23150778, PMC3495282
- Conway JO, Sherwood LJ, Collazo MT, Garza JA, **Hayhurst A**. Llama single domain antibodies specific for the 7 botulinum neurotoxin serotypes as heptaplex immunoreagents. *PLoS One* 2010, Jan 21;5(1) PMID:20098614, PMC 2809108

A complete list of publications can be found at www.ncbi.nlm.nih.gov/pubmed/?term=Hayhurst+A

JOHN (JACK) W. KENT, JR, PH.D.

STAFF SCIENTIST III, GENETICS

RESEARCH FOCUS

Dr. Kent focuses on development and implementation of computational tools for the analysis of complex genomic data. He is interested in applying these tools to help understand the causes of diverse, complex phenotypes. This includes scientific collaborations with investigators at Texas Biomed and in other institutions on the integration of multiple levels of genomic, transcriptomic, and epigenetic data.

Dr. Kent has 20 years of expertise in quantitative genetics.

INSIDE THE LAB

Much of our current work focuses on methods for integrating multiple levels of data reflecting gene action (genomic, epigenetic, transcriptomic, proteomic, and metabolomic) as well as gene by environment interaction. A goal is to extend Texas Biomed's traditional expertise in genetic analysis of pedigreed individuals to consideration of genomic similarity at functionally-defined regions in a variety of study designs for human and non-human model organisms.

In addition to collaborative projects, my own funded research focuses on identification of early biomarkers of diabetic kidney disease.

MAIN TECHNOLOGIES AND METHODS USED

- Parallel processing capacity of the AT&T Genomics Computing Center
- Variance components analysis (SOLAR, kinship2)
- Pedigree data management in PEDSYS
- Development of pipelines (e.g, Galaxy) for alignment and annotation of sequence data

PUBLICATIONS

- **Kent JW Jr**, Göring HHH, Charlesworth JC, Drigalenko E, Diego VP, Curran JE, Johnson MP, Dyer TD, Cole SA, Jowett JB, Mahaney MC, Comuzzie AG, Almasy L, Moses EK, Blangero J, Williams-Blangero S. Genotype × age interaction in human transcriptional ageing. *Mech Ageing Dev* 2012 Sep-Oct;133(9-10):581-90. PMID: 22871458, PMC3541784
- Zhang Y, **Kent JW Jr**, Olivier M, Ali O, Cerjak D, Broeckel U, Abdou RM, Dyer TD, Comuzzie A, Curran JE, Carless MA, Rainwater DL, Göring HHH, Blangero J, Kissebah AH. A comprehensive analysis of adiponectin QTLs using SNP association, SNP cis-effects on peripheral blood gene expression and gene expression correlation identified novel metabolic syndrome (MetS) genes with potential role in carcinogenesis and systemic inflammation. *BMC Med Genomics* 2013 Apr 29;6:14. PMID: 23628382, PMC3643849
- Kulkarni H, Kos MZ, Neary J, Dyer TD, **Kent JW Jr**, Göring HHH, Cole SA, Comuzzie AG, Almasy L, Mahaney MC, Curran JE, Blangero J, Carless MA. Novel epigenetic determinants of type 2 diabetes in Mexican-American families. *Hum Mol Genet* 2015;24:5330-5344. PMID: 26101197, PMC4550817

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47946602/?sort=date&direction=asce

ROBERT LANFORD, PH.D.

DIRECTOR, SNPRC

SCIENTIST, VIROLOGY AND IMMUNOLOGY

RESEARCH FOCUS

Dr. Lanford is Director of the Southwest National Primate Research Center. SNPRC is one of the seven NIH-funded National Primate Research Centers. The Center focuses on the development and use of nonhuman primate models of human diseases. Dr. Lanford and Dr. John Bernal are also the Principal Investigators of the U42 grant "Establishment of a SPF Rhesus Macaque Colony" that provides animals for AIDS research.

His scientific focus is on hepatitis viruses, especially how viral-host interactions and innate immune response influence disease progression.

- Primate models of liver disease
- Hepatitis B virus (HBV)
- Hepatitis C virus (HCV)
- GB virus-B (GBV-B), a surrogate model for HCV
- Liver cancer

Dr. Lanford has more than 40 years expertise as virologist.

INSIDE THE LAB

In a multi-team effort, we studied the mechanism of viral clearance and persistence by comparing infections with two viruses: HCV (a virus that frequently causes chronic infections) and HAV (a virus that is always cleared by the immune system). These studies highlighted the differences in innate immune response and the CD4+ T cell response in these two models.

Our lab pioneered the use of total genome microarrays to examine the innate immune response in the liver to HCV infection. In our chimpanzee studies, we demonstrated that specific liver gene expression patterns during chronic infection correlate with a lack of efficacy to interferon therapy, later recognized in humans as the Null Responder Phenotype. These studies initiated the use of microarrays in the field of hepatitis, defined the interferon stimulated gene response (ISG), and provided insight into the basis for the Null Responder Phenotype to interferon in chimpanzees and humans.

We have been involved in the testing of new antiviral therapies for the treatment of chronic hepatitis infections. My group collaborated with more than 20 biotech and pharmaceutical companies to examine the safety and efficacy of HCV antivirals in the chimpanzee model as the last preclinical step prior to human trials. Today, two antiviral cocktails are FDA approved and others are near approval that can cure HCV with 12 weeks of daily oral medications. SNPRC helped develop one of the FDA-approved cocktails with safety and efficacy studies that spanned a 10-year period.

One of the novel inhibitors of HCV that we examined involved inhibition of a molecule in the liver required by the virus for replication. This inhibitor sequestered a liver-specific microRNA called miR122. The drug Miravirsen is a Locked Nucleic Acid (LNA) antisense oligonucleotide. This was the first example of a DNA-based therapy that is highly efficacious when administered systemically. Our proof-of-concept study demonstrated the feasibility of treating other diseases using LNA technology, including cancer and inflammatory diseases.

In collaboration with Gilead, we examined a toll-like receptor 7 (TLR7) agonist in HBV therapy; it induced the innate immune response and triggered activation of the adaptive immune response during chronic infection, to eliminate infected cells. This compound is currently in human clinical trials for HBV. Our recently completed studies with Arrowhead use a novel siRNA that targets HBV in the liver and presents a very promising therapy that has also progressed to human clinical trials.

We are currently working on the development of several new primate models for liver disease. One area of interest is the development of a small primate model for HBV chronic infection to replace the chimpanzee model. A second project involves the development of a baboon model for liver cancer. Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide, and HCC has become the most rapidly increasing cause of death due to cancer in the U.S., primarily attributable to the HCV epidemic. We have created a model of liver cancer in the baboon by genetic engineering of liver cells, hepatocytes, *in vitro* and implantation of the cells back into the liver of the donor baboon. Tumor development occurs in 1-3 months, rather than after decades of chronic hepatitis. We are currently using this model to explore novel therapeutics in collaboration with the biotech industry.

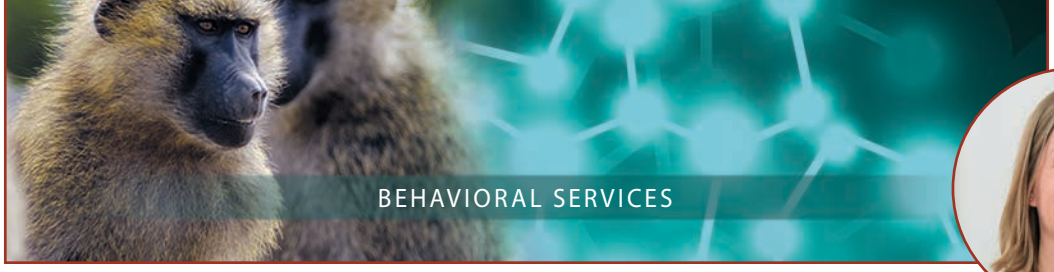
MAIN TECHNOLOGIES AND METHODS USED

- Nonhuman primate model development
- Gene expression using microarrays and qRT-PCR
- Primary hepatocyte technology
- Lentivirus expression vectors with oncogenes

PUBLICATIONS

- **Lanford RE**, Hildebrandt-Eriksen ES, Petri A, Persson R, Lindow M, Munk ME, Kauppinen S, Orum. H. Therapeutic silencing of microRNA-122 in primates with chronic hepatitis C virus infection. Science 2010; 8;327:198-201. PMID: 19965718, PMC19965718
- **Lanford RE**, Guerra B, Chavez D, Giavedoni L, Hodara VL, Brasky KM, Fosdick A, Frey CR, Zheng. J, Wolfgang G, et al. GS-9620, an oral agonist of Toll-like receptor-7, induces prolonged suppression of hepatitis B virus in chronically infected chimpanzees. Gastroenterology 2013;144(7):1508-1517. PMC23415804
- Feng Z, Hensley L, McKnight KL, Hu F, Madden V, Ping L, Jeong SH, Walker C, **Lanford RE**, Lemon SM. A pathogenic picornavirus acquires an envelope by hijacking cellular membranes. *Nature*. 2013 Apr 18;496(7445):367-71. doi: 10.1038/nature12029. Epub 2013 Mar 31. PMID: 23542590, PMC3631468.

A complete list of publications can be found at wsw.ncbi.nlm.nih.gov/myncbi/browse/collection/40344892/?sort=date&direction



CORRINE LUTZ, PH.D.

DIRECTOR OF BEHAVIORAL SERVICES, SNPRC

RESEARCH FOCUS

Dr. Lutz is the director of Behavioral Services at SNPRC and an active member of the National Primate Research Centers' Behavioral Management Consortium. She has more than 25 years of experience in the study of non-human primate behavior.

The Behavioral Services program's mission is threefold:

- Provide high quality of life to SNPRC non human primates through enrichment, training, socialization, behavioral intervention, and staff education
- Increase knowledge and understanding of the behavior of non-human primates
- Advance state-of-the-art behavioral management practices for the promotion of animal welfare

RESEARCH SUPPORT

All animals are provided with **Environmental Enrichment**, which includes structural, manipulable, nutritional, occupational, sensory, and social enrichment. Enrichment devices or procedures are routinely assessed for effectiveness. A social partner is perhaps the most important form of enrichment because the partner provides constantly changing stimuli and challenges the social and cognitive functioning of the animal. Therefore, most of the non-human primates at SNPRC are housed in pairs or social groups.

Colony management. The Behavioral Services team provides a range of additional services for colony management and research. For example, Behavioral Services staff members train animals to cooperate for routine husbandry, research, and clinical procedures. They also work to form compatible pairs and social groups, and they conduct routine observations on many of the animals to assess their compatibility and well-being. If an animal has special needs, a behavioral intervention plan will be instituted.

Staff education is of great importance for optimal, state-of-the-art animal care, and Behavioral Services teaches eight classes that cover the topics of animal training, alopecia, primate behavior, and environmental enrichment. Behavioral Services personnel also consult with investigators whose projects may be affected by the behavioral abilities, needs, and limitations of study animals. They make recommendations for the selection of animals for any given project, collect relevant behavioral data, and design optimal procedures to minimize animal stress.

RESEARCH INTERESTS

Dr. Lutz's research interests broadly include the following areas:

- Environmental enrichment
- Behavior of non human primates
- Effects of captive housing on behavior
- Alopecia

Behavior of non human primates. Dr. Lutz's main research interest is the study of abnormal behavior in captive non human primates. Abnormal behavior may be an indicator of either past or present environmental deficits, and treatment methods are not always effective. Because behavioral problems can negatively impact both research and animal welfare, the focus of her work is to examine the extent of abnormal behavior in captive non-human primate populations and identify risk factors with an aim towards prevention. Common risk factors have been identified, and include nursery rearing, single housing, and sedation events. This information is utilized to direct and improve animal management practices.

Alopecia (hair loss). Alopecia is a common occurrence in primate populations, and hair loss can range from small focal areas to large portions of the body. Various conditions are associated with hair loss in non-human primates. These may include pregnancy, stress, aging, behavior (e.g., pulling hair from self or others), disease, housing condition, social rank, and seasonal molting. Although the true impact of hair loss on animal welfare is unknown, it may serve as indicator of underlying conditions that affect an animal's wellbeing. Dr. Lutz is currently investigating alopecia in a cross-facility collaboration to identify the extent of hair loss in primate populations and to identify risk factors with an aim to better understand its impact on animal welfare.

Physiological measures of stress. Dr. Lutz utilizes measures of cortisol as an indicator of stress. She developed a method of collecting saliva samples from awake, unrestrained rhesus monkeys and utilized this technique to assess the relationship between salivary cortisol and self-injurious behavior. Dr. Lutz currently utilizes cortisol obtained from hair samples as a measure of chronic stress to assess its association with abnormal behavior, alopecia, and environmental conditions.

PUBLICATIONS

- **Lutz CK**, Coleman K, Worlein J, Novak MA. Hair loss and hair-pulling in rhesus macaques (Macaca mulatta). *J Am Assoc Lab Anim Sci* 2013 Jul;52(4):454-7. PubMed PMID: 23849443, PMC3725930
- **Lutz CK**. Stereotypic behavior in non-human primates as a model for the human condition. *ILAR J* 2014;55(2):284-96. PMID: 25225307, PMC4240438
- **Lutz CK**, Williams PC, Sharp RM. Abnormal behavior and associated risk factors in captive baboons *(Papio hamadryas spp.). Am J Primatol* 2014; 76(4):355-61. NIHMSID: NIHMS663770 PMID: 24323406, PMC4346173

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47539379/?sort=date&direction=ascending

MICHAEL OLIVIER, PH.D.

SCIENTIST AND CHAIR, GENETICS

RESEARCH FOCUS

Dr. Olivier has more than 20 years of expertise in genomics and technology development in both genomics and proteomics. His efforts focus on the design of better tools to study, understand, and ultimately treat human disorders. Dr. Olivier's research explores how variations in our genome sequence affect the structure, function, and expression of proteins, to help develop new approaches for treating complex disorders like diabetes, obesity, and heart disease.

His work utilizes both human patient samples and non-human primate models of complex human diseases, with a special emphasis on obesity and associated lipid disorders, including characteristic cholesterol abnormalities in patients with the metabolic syndrome, and non-alcoholic fatty liver disease. His research has uncovered novel genes and gene variants contributing to abnormal lipid profiles in humans.

- **Diseases:** Metabolic syndrome, heart disease, diabetes, obesity, non-alcoholic fatty liver disease
- Technology development in genomics and proteomics
- Discovery of novel genes and gene variants

Dr. Olivier is Director of the Wisconsin Center of Excellence in Genomics Science (CEGS) and Co-Director of the recently established TOPS Nutrition and Obesity Research Center in the Department of Genetics at Texas Biomed.

INSIDE THE LAB

Proteomics and genomics approaches. We use proteomics approaches to complement genetic analyses in a wide range of human disorders, e.g. the analysis of lipoprotein particles isolated from human plasma, or liver biopsy samples from patients with non-alcoholic fatty liver disease. Our group has optimized proteomics analyses in non-human primate samples by using RNA-Seq data for improved protein identification in cells and tissues.

We have been developing novel technologies for the comprehensive characterization of proteins interacting with DNA and chromatin. Our work has resulted in a new approach called Hybridization Capture of Chromatin-Associated Proteins for Proteomics (HyCCAPP). This methodology enables the analysis of individual gene regions or promoter intervals, and the characterization of the bound proteins by mass spectrometry without any prior knowledge of binding proteins, or available antibodies. We are currently characterizing the effect of disease- and gene expression-associated promoter sequence variants on protein binding and promoter regulation.

Since the proteome is highly complex, we have been working on optimizing methodologies to help the quantitative characterization of cellular proteomes, including cost-effective isotopic labeling approaches and the analysis of posttranslational modifications.

TOPS (Take Off Pounds Sensibly) is a large, non-profit weight loss support organization headquartered in Milwaukee, WI, with chapters across the entire U.S. TOPS has supported obesity research for several decades. As part of a large-scale genetic study, the Metabolic Risk Complications of Obesity (MRC-OB) Genes Study, our research focused on the analysis of the genetic contributions to obesity-related co-morbidities, especially elevated plasma triglyceride levels, a risk factor for cardiovascular disease. We conducted extensive fine-mapping and single nucleotide polymorphism (SNP) analyses for obesity-related lipid traits.

Discussions with the TOPS leadership explored unique opportunities for obesity and nutrition research here in San Antonio, culminating in a new TOPS Nutrition and Obesity Research Center in the Department of Genetics at Texas Biomed that I co-direct with my fellow scientist, Dr. Tony Comuzzie. The Center's research efforts will focus on the contribution of genetic and lifestyle factors on the development of obesity, and the ability to lose weight successfully.

Non-human primate models. Thanks to the SNPRC, my group has started novel programs to utilize non-human primate models in comparative studies of obesity and the metabolic syndrome. This includes the comprehensive analysis of changes in the liver as a result of dietary challenges or aging. Here, we integrate genomic, proteomic, and metabolic profiling to explore the complex networks of genes and pathways mediating the physiological changes. In a different study, we are developing methodologies to use both next generation sequencing and proteomic analyses to characterize the gut microbiome of non-human primates, and explore how the composition and activity of the gut flora fluctuates with changes in nutrition.

MAIN TECHNOLOGIES AND METHODS USED

- Illumina DNA sequencing
- Chromatin Immunoprecipitation (ChIP) sequencing
- SNP genotyping
- HyCCAPP
- Protein mass spectrometry
- Induced pluripotent stem cell models

PUBLICATIONS

- Kennedy-Darling J, Guillen-Ahlers H, Shortreed MR, Scalf M, Frey BL, Kendziorski C, **Olivier M,** Gasch AP, and Smith LM. Discovery of chromatin-associated proteins via sequence-specific capture and mass spectrometric protein identification in *Saccharomyces cerevisiae*. *J Prot Res* 2014, 13(8): 3810-25. PMID: 24999558, PMC4123949
- Indap AR, Cole R, Runge CL, Marth GT, and **Olivier M.** Variant discovery in targeted resequencing using whole genome amplified DNA. *BMC Genomics* 2013, 4:468. doi: 10.1186/1471-2164-14-468. PMC3716764

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/1Zi2frtrkyPAX/bibliograpahy/9879103/public/?sort=date&direction=ascending

MICHAEL OWSTON, D.V.M.

ASSOCIATE VETERINARIAN AND VETERINARY PATHOLOGIST, SNPRC

RESEARCH FOCUS

Dr. Owston is a board-certified Veterinary Anatomic Pathologist. He has 10 years of expertise in anatomic pathology and is highly skilled in working with a wide range of domestic and laboratory animal species. For the past six years he has been working at SNPRC where he provides pathology services for the baboons, marmosets, macaques, and chimpanzees. His responsibilities include the oversight of the clinical and anatomic pathology laboratories.

Dr. Owston's current scientific contributions encompass support of research protocols, support for colony health, and advancements in diagnostic pathology.

Examples of his pathology supports for scientists include:

- Detailed analysis of GLP-1 analogues on primate pancreas pathology
- Development of a neonatal macaque tuberculosis model
- Identification of *Trypanosoma cruzi* in infected monkeys
- Investigations into high fat diet effects on primates

Dr. Owston has been collaborating on the development of several diagnostic assays designed to:

- Detect reovirus infections in baboons
- Immunohistochemically type gonadal tumors
- Genotype bacterial isolates

Previous laboratory research resulted in publications on the analysis of inhibitors of viral replication in yellow fever virus, and on conformations of aminoglycoside antibiotics in the active sites of bacterial antibiotic resistance enzymes.

Dr. Owston has co-authored a number of publications with scientists at SNPRC and elsewhere who utilize the SNPRC resources.

MAIN TECHNOLOGIES AND METHODS USED

- Gross pathology in ABSL-2, ABSL-3, and ABSL-4
- Histopathology
- Clinical chemistry and hematology
- Cytology
- Immunohistochemistry
- ELISA
- Basic molecular biology techniques
- Fluorescent microscopy

PUBLICATIONS

- Fiorentino TV, **Owston MA**, Abrahamian G, La Rosa S, Marando A, et al. Chronic continuous exenatide infusion does not cause pancreatic inflammation and ductal hyperplasia in non-human primates. *Am J Pathol* 2015, 185(1):139-50. PMID: 25447052, PMC4278248
- Kumar S, Dick EJ Jr, Bommineni YR, Yang A, Mubiru J, Hubbard GB, **Owston MA**. Reovirus-Associated Meningoencephalomyelitis in Baboons. *Vet Pathol* 2014, May;51(3):641-50. PMC3964136
- Dick EJ Jr, **Owston MA**, David JM, Sharp RM, Rouse S, et al. Mortality in captive baboons (Papio spp.): a-23-year study. *J Med Primatol* 2014, 43(3):169-96. NIHMSID: NIHMS553896; PMID:24483852, PMC3989440

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/42110166/?sort=&direction=

JEAN PATTERSON, PH.D.

CHAIR, BSL-4 TASK FORCE
SCIENTIST, VIROLOGY AND IMMUNOLOGY

RESEARCH FOCUS

Dr. Patterson's laboratory works on the development of countermeasures against potential biological weapons. Her group focuses on the development of therapies and vaccines against naturally occurring pathogens that can cause sporadic but lethal outbreaks, and her most recent studies concentrate on hemorrhagic fever viruses. Dr. Patterson has been involved in the development of three vaccines against Ebola and two vaccines against Lassa fever that are undergoing further studies.

Her lab utilizes the maximum containment laboratory (BSL-4) at Texas Biomed.

Dr. Patterson helped develop a marmoset model used for multiple infectious agents:

- Ebola virus
- Marburg virus
- Lassa fever
- Eastern Equine Encephalitis virus

INSIDE THE LAB

My laboratory has worked on the development of countermeasures against many select agents. This involved the development of three vaccines against Ebola, one with Emory University, one with Crucell (Janssen Pharmaceuticals), and one with Bavarian Nordic, all of which are undergoing further studies. The Department of Defense and NIH are committed to an Ebola and Marburg vaccine, and our lab is working with them toward this goal.

We have also worked with the University of Maryland on the development of two vaccines against Lassa fever, a hemorrhagic fever that causes serious outbreaks in West Africa. The zoonotic, single-stranded RNA virus responsible for Lassa fever (family *Arenaviridae*) causes infections in more than 500,000 persons every year, resulting in a roughly 10 percent fatality rate and many different forms of lasting health effects.

In collaboration with Dr. Ricardo Carrion, Jr. in our department, our lab developed the marmoset as a model for many infectious agents. Thanks to its size and behavior, this small non-human primate is a much better model organism than other larger, more aggressive non-human primates. To date, we have utilized the marmoset for the model development of Eastern Equine Encephalitis virus, Lassa fever virus, Ebola virus, and Marburg virus. The marmoset is an important model for our work, since the pathogenesis of these viral diseases in marmosets closely mimics that of human disease.

Our group worked with Dr. Charles Chui (UCSF) and identified a novel adenovirus associated with baboons (SAdV-C) in an acute respiratory outbreak in a baboon colony, which underscores the potential for cross-species transmission of adenoviruses between humans and non-human primates.

We are also working on the development of detection assays using novel technologies. One of the newest technologies is optofluidic analysis for amplification of free, direct detection of Ebola infection.

MAIN TECHNOLOGIES AND METHODS USED

- Non human primate model (marmoset)
- Viral growth requirements and particle characterization
- Novel diagnostic technologies
- Determination of vaccine efficacy

PUBLICATIONS

- Alfson KJ, Avena LE, Beadles MW, Staples H, Nunneley JW, Ticer A, Dick EJ Jr, Owston MA, Reed C, **Patterson JL**, Carrion R Jr, Griffiths A. Particle-to-PFU ratio of Ebola virus influences disease course and survival in cynomolgus macaques. *J Virol* 2015, 89(13):6773-81. PMID:25903348, PMC4468478
- Li W, Ye L, Carrion R Jr, Mohan GS, Nunneley J, Staples H, Ticer A, **Patterson JL**, Compans RW, Yang C. Characterization of immune responses induced by ebola virus glycoprotein (gp) and truncated gp isoform dna vaccines and protection against lethal ebola virus challenge in mice. *J Infect Dis* 2015; 212 Suppl 2:S398-403. PMID:25877553, PMC4564543
- Chiu CY, Yagi S, Lu X, Yu G, Chen EC, Liu M, Dick EJ Jr, Carey KD, Erdman DD, Leland MM, **Patterson JL**. A Novel adenovirus species associated with an acute respiratory outbreak in a baboon colony and evidence of coincident human infection. *MBio* 2013; 4(2):e00084. PMID: 23592261, PMC3634605

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/jeanl..patterson,phd.1/bibliography/40468610/public/?sort=date&direction=ascending

JERILYN K. PECOTTE, PH.D.

STAFF SCIENTIST III, SNPRC

RESEARCH FOCUS

Dr. Pecotte has a broad background in biological anthropology and additional training in human anatomy. She is specialized in forensic anthropology and has worked as consultant in this field in the US and Italy. Dr. Pecotte has been a member of the International Society for Biological and Environmental Repositories (ISBER) for more than five years.

As head of the Biomaterials Services for the past 13 years, Dr. Pecotte has been providing crucial support to multiple research projects at Texas Biomed. Her recent focus is on:

- Collecting and distributing tissues for individual scientific projects from the Repository, necropsies, and animals sedated for other purposes
- Maintaining a database of requests and final distribution of tissues using the new program Freezerworks
- Providing scientists with archived chimpanzee samples from decades of research.

INSIDE THE LAB

Dr. Pecotte is head of tissue share and provides recommendations for the selection of different species and tissue types to aid investigators in optimizing their design of research projects.

To streamline sample information and acquisition, she configured the framework for a new freezer inventory database software (Freezerworks), which included the data import for approximately 88,000 existing samples. By now, all of the SNPRC is using Freezerworks combined with management software (LabKey), which allows investigators to more easily access sample information from multiple databases.

Through her work, Dr. Pecotte regularly contributes to the successful publication of peer-reviewed scientific papers.

One example of her contributions is her supply of tissues to Dr. Michiko Fukada (Sanford-Burnham Medical Research Institute, La Jolla, CA) since 2009, who was interested in developing new treatments for endometriosis. Dr. Pecotte suggested on focusing on baboons rather than rhesus monkeys (although both spontaneously develop endometriosis), since SNPRC had a larger baboon colony and could more quickly collect the necessary specimens of tumor and endometrial tissue. Moreover, technicians at the SNPRC have been trained to recognize the stages of the baboon menstrual cycle, so cycle stage could be determined. In 2014, Dr. Fukada published the results of the work after performing a project at the SNPRC as proof of concept.

In 2009, Dr. Margo Brinton (Georgia State University) requested blood from wild-caught baboons to screen for simian hemorrhagic fever virus (SHFV). She then was able to trace the virus by serial serum collections on living wild-caught animals that tested positive. Dr. Pecotte collected information from archived records to determine the origin of the wild-caught animals and whether they were housed with other colony-born animals who screened as positive. This documentation and tissue archiving provided information to hypothesize about transmission of this virus to colony-born animals. The study resulted in two recent publications (2014 and 2015) on the characterization and spread of SHFV. An additional publication by a separate group (Bailey et al., 2014), confirmed the presence of the virus in the colony.

PUBLICATIONS

- Vatter HA , Donaldson EF, Huynh J, Rawlings S, Manoharan M, Legasse A, Planer A, Dickerson MF, Lewis AD, Colgin LMA, Axthelm MK, **Pecotte JK**, Baric RS, Wong SW and Brinton MA. A simian hemorrhagic fever virus isolate from persistently infected baboons efficiently induces hemorrhagic fever disease in Japanese macaques. *Virology*, 2015 Jan 1; 474:186-98. NIHMS640352, PMC4304765.
- Sugihara K, Kobayashi Y, Suzuki A, Tamura N, Motamedchaboki K, Huang C-T, Akama TO, **Pecotte JK**, Frost P, Bauer C, Jimenez JB, Nakayama J, Aoki D, Fukada MN. Development of pro-apoptotic peptides as potential therapy for peritoneal endometriosis. *Nat Commun* 2014, Jul 22; 5:4478. NIHMS607615, PMC4109024
- Michels R, **Pecotte JK**. Better Mousetrap: Getting Cap labels to stick in liquid nitrogen and vial transfer. *ISBER News* 2014, Feb Vol 14, No.1, Page 11

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/jerilyn.pecotte.1/bibliography/47759218/public/?sort=date&direction=ascending

KAREN RICE, PH.D.

ASSISTANT DIRECTOR OF RESEARCH RESOURCES, SNPRC

RESEARCH FOCUS

Dr. Rice is the Assistant Director of Research Resources for SNPRC, leading two components within the Primate Center:

- Baboon colony
- Research coordination

Dr. Rice serves as a liaison to help with coordination between the scientist sponsor and the resources provided by the SNPRC. Since the SNPRC houses more than 2,400 nonhuman primates of different species, it provides a unique setting to address a multitude of highly diverse research needs.

RESEARCH COORDINATION

As leader of the Research Coordination component, Dr. Rice has collaborated with many local, national, and international investigators from diverse scientific backgrounds, focused on cardiovascular, metabolic, and infectious diseases, reproduction, medical devices, and cancer.

For more than 30 years, she has also been working with investigators on aging, bone biology, diseases of the pre-term infant, gene therapy, vaccine development, and reproductive biology, while providing advice on species selection for optimal animals for experiments with intensive selection criteria.

Her extensive experience in research management embraces animal selection procedures, animal protocol development, and implementation. In her work, she is supported by a skilled team of research coordinators in the SNPRC who assist with budgets, timelines, schedules, and project monitoring.

BABOON COLONY MANAGEMEN

Dr. Rice has been involved in baboon colony management for more than 25 years, and she has been associated with NIH-funded studies on the diet and genotype in primate atherosclerosis since she began her career at Texas Biomed in 1985.

Dr. Rice was also involved with an NHLBI contract for 10 years that provided modeled baboons for outside researchers, and has been continuing this work. In 2007, she became the Veterinary Services Core Unit Leader for a program project grant and became the leader for the Baboon Colony at the Primate Center in 2008. These experiences have prepared her for continued leadership of the SNPRC Baboon Colony Component.

PUBLICATIONS

- Brunetti-Pierri N, Ng T, Iannitti D, Cioffi W, Stapleton G, et al. Transgene expression up to 7 years in nonhuman primates following hepatic transduction with helper-dependent adenoviral vectors. *Hum Gene Ther* 2013, 24(8):761-5. PMID: 23902403, PMC3746245.
- Higgins PB, Rodriguez PJ, Voruganti VS, Mattern V, Bastarrachea RA, et al. Body composition and cardiometabolic disease risk factors in captive baboons *(Papio hamadryas sp.)*: sexual dimorphism. *Am J Phys Anthropol* 2014, 153(1):9-14 NIHMS570689 PMID: 24318937, PMC4025923
- Shi Q, Hodara V, Meng Q, Voruganti VS, **Rice K**, et al. Early endothelial damage detected by circulating particles in baboons fed a diet high in simple carbohydrates in conjunction with saturated or unsaturated fat. *Am J Cardiovasc Dis* 2014, 4(3):123-32. PMID: 25360390, PMC421288

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/47758829/?sort=date&direction=ascending

RUTH RUPRECHT, M.D., PH.D.

SCIENTIST, VIROLOGY AND IMMUNOLOGY
INFECTIOUS DISEASE UNIT LEADER, SNPRC
DIRECTOR, TEXAS BIOMED AIDS RESEARCH PROGRAM

RESEARCH FOCUS

HIV infections continue to be a global health threat, and there is still no vaccine or cure available. Dr. Ruprecht's research is focused on lentiviruses such as HIV, where she develops strategies for treatment and prevention. Her special interest is to develop vaccines against HIV/AIDS, particularly against the world's most prevalent subtype of HIV (HIV-C) in Sub-Saharan Africa and India. Her research strategy is to:

- Develop vaccines to block HIV at portals of entry: mucosal sites
- Construct multi-component vaccines that enlist as many host defense mechanisms as possible

Dr. Ruprecht was the first to demonstrate the *in vivo* safety and efficacy of AZT drug treatment in animal models, including prevention of maternal virus transmission. AZT later became the first FDA-approved AIDS drug and the first drug to prevent HIV transmission from an infected woman to her newborn. Dr. Ruprecht has been collaborating with scientists in the US, Europe, Asia and Africa, and is now Director of Texas Biomed's AIDS research program. She has been studying lentiviruses since the discovery of HIV and has worked with non-human primate (NHP) models for more than 25 years.

INSIDE THE LAB

Understanding mucosal virus transmission and vaccine development. One current research focus is on understanding mucosal virus transmission and its prevention, since 90 percent of all new HIV infections occur through mucosal exposure. To study anti-HIV-C envelope responses in NHP models, we have generated a panel of chimeric simian-human immunodeficiency virus (SHIV) strains that encode envelopes of recently transmitted HIV-Cs. The resulting SHIV-Cs are pathogenic, and one such infectious molecular clone was used to measure how easily different mucosal barriers can be penetrated in rhesus macaques. The relative mucosal permeability in the primate model paralleled the relative risks of HIV acquisitions in humans exposed to virus by different routes, thus confirming the SHIV-C model as a biologically relevant tool.

A protective anti-HIV vaccine needs to be not only bimodal — able to induce both cellular and humoral immunity — but also protect the mucosal barrier. We are actively pursuing such a "defense-in-depth" strategy. Using recombinant viral proteins as immunogens, we induced high levels of specific T cells and cross-neutralizing antibodies (Abs) in some vaccinated rhesus macaques. When challenged mucosally with SHIV-C carrying a heterologous *env* gene, some rhesus macaques were completely protected. Neutralizing Ab titers and cellular immune responses were significant correlates of protection.

To protect the mucosal barrier, we focused on IgA Abs in mucosal fluids, where these molecules exist in dimeric form. We provided the first direct proof that dimeric IgAs targeting the HIV envelope and delivered mucosally can protect rhesus macaques against mucosal virus challenge. A vaccine that could stimulate strong mucosal IgA responses against HIV would have a significant impact on transmission rates.

We have also developed a novel strategy to identify the protein regions in a vaccine that are exclusively recognized by Abs from rhesus macaques protected by vaccination — but not by Abs from rhesus macaques where the vaccine had failed. Using our new tool (termed differential biopanning), we have identified an Ab target outside the virus envelope that was significantly linked to vaccine protection. This new approach is attractive to refine vaccine design, even beyond HIV/AIDS vaccine development or infectious disease.

Our lab also developed the technology to isolate epitope/mimotope-specific monoclonal Ab (mAbs) from single rhesus monkey memory B cells collected by flow cytometry. This new approach utilizes fusion proteins linked to green fluorescent protein. These new technologies could lead to the isolation of novel recombinant mAbs for clinical use.

Mother-to-child transmission (MTCT). Primate models have played an essential role in our work; this includes studying the interaction of lentiviruses with the developing immune system in the fetus and newborn. Our long-term goal is to prevent HIV MTCT by effective antiviral drugs as well as by enlisting immune defenses, and we utilized infant rhesus monkey models with SIV or SHIV in our studies. We provided proof-of-principle for the:

a) Pathogenicity of live attenuated, *nef*-deleted SIV when used as a vaccine in neonatal RMs; this finding was confirmed later also in adult RMs

b) Protection of neonatal RMs against oral SHIV transmission with a combination of neutralizing human monoclonal Abs — even when given as post-exposure prophylaxis (PEP)

c) Time dependence of successful PEP

Our current goal is to determine whether candidate AIDS vaccines, partnered with antiviral drugs, will not only completely suppress HIV replication in babies infected with HIV at birth, but will also induce such strong antiviral cellular immune defenses that the virus will not reemerge after all treatment is stopped. We will test our concepts in infant and neonatal rhesus macaques. These primate models will allow us to assess whether the virus can be cleared from tissue reservoirs and whether long-lasting protective immunity has been generated by the combined treatment.

MAIN TECHNOLOGIES AND METHODS USED

- Cloning, production and purification of monoclonal Abs
- RT-PCR
- Sequencing to study viral evolution
- Passive and active immunization in primate models
- Flow cytometry
- Virus transcytosis
- Assays for cell-mediated and humoral immune responses

PUBLICATIONS

- Sholukh AM, Watkins JD, Vyas HK, Gupta S, Lakhashe SK, Thorat S, Zhou M, Hemashettar G, Bachler BC, Forthal DN, Villinger F, Sattentau QJ, Weiss RA, Agatic G, Corti D, Lanzavecchia A, Heeney JL, **Ruprecht RM**. Defense-in-depth by mucosally administered anti-HIV dimeric IgA2 and systemic IgG1 mAbs: complete protection of rhesus monkeys from mucosal SHIV challenge. *Vaccine* 2015; 33(17):2086-95. NIHMSID: NIHMS671514 PMID:25769884, PMC4411954
- Watkins JD, Sholukh AM, Mukhtar MM, Siddappa NB, Lakhashe SK, Kim M, Reinherz EL, Gupta S, Forthal DN, Sattentau QJ, Villinger F, Corti D, **Ruprecht RM**; CAVD Project Group. Anti-HIV IgA isotypes: differential virion capture and inhibition of transcytosis are linked to prevention of mucosal R5 SHIV transmission. *AIDS* 2013 Jun 1;27(9):F13-20. doi: 10.1097/QAD.0b013e328360eac6. PMID:23775002, PMC4084966

A complete list of publications can be found at www.ncbi.nlm.nih.gov/myncbi/browse/collection/41154239/?sort=date&direction=ascending

SUZETTE D. TARDIF, PH.D.

SCIENTIST AND ASSOCIATE DIRECTOR OF RESEARCH, SNPRC

RESEARCH FOCUS

Dr. Tardif is Associate Director of Research and Senior Management Team member for SNPRC and has extensive experience coordinating large, integrated research projects throughout her professional career. She served as the marmoset expert for the team charged with sequencing the marmoset genome and as the species expert for recent studies on development of induced pluripotent stem cell (iPS cell) technologies.

Her research is focused on metabolism, behavior and reproduction and, most recently, on the characterization of the marmoset as a model for obesity and aging.

Dr. Tardif has more than 30 years of expertise in the development of common marmoset monkeys as biomedical models in diverse areas including:

- Reproductive biology
- Infectious disease
- Neuroscience
- Aging and obesity

INSIDE THE LAB

Pediatric obesity. My laboratory has identified and characterized the first, spontaneous model of pediatric obesity in a nonhuman primate (NHP). The common marmoset is the only nonhuman primate demonstrated to routinely become obese early in life. This pediatric obesity is associated with high growth rates of both lean and fat mass, similar to the common pattern of human pediatric obesity, with earlier weaning to solid food, and with differences in post-weaning feeding behavior. While marmoset pediatric obesity occurs spontaneously (without the feeding of high fat diets), the availability of a diet that includes high-fat choices increases the occurrence of marmoset pediatric obesity and causes obesity to be prevalent earlier in infancy. This early-life obesity in marmosets is associated with evidence of insulin resistance, mirroring the effects of early life obesity in human children. Our findings point to the common marmoset as a valuable tool to study obesity, particularly pediatric obesity.

Aging. Our group studies the effect of aging interventions on the healthspan and lifespan of a primate.

We have developed the marmoset as an efficient model to study NHP aging. The use of the marmoset as a nonhuman animal model to screen aging interventions represents a major innovation in aging research and allows investigators to test the effects of interventions in a primate in a relatively short time at reasonable costs.

The marmoset is the only commonly used NHP model in which longitudinal studies of adequate life span expanse can be conducted within a five-year period. The Intervention Testing Program of the Barshop Institute reported in 2009 on the first pharmaceutical intervention to reliably increase lifespan in a rodent model, (touted as one of the top 10 scientific discoveries of 2009 by *Science*). Translation of this important finding to improving human health depends on testing for both efficacy and side-effects in a model more closely related to humans. The SNPRC and Barshop Institute collaborated in a study on the effects of a 14-month exposure to Rapamycin in marmosets. Our groups were able to rapidly and reliably dose socially housed marmosets with a well-tolerated oral form of Rapamycin that results in suppression of the mTOR pathway and that indicates no increased risk for hyperglycemia or insulin resistance.

Genome sequencing. To expand the common marmoset as a valuable research model, we need to develop new cellular and molecular tools specific for this species. The process of selection of the marmoset for genome sequencing was initiated with submission of a white paper co-authored by me, and I provided the material used for the sequencing and served as the species expert on the panel that assessed notable findings from the genome sequence, including a possible basis for the evolved miniaturization in this species, a refined understanding of the evolution of primate microRNAs, and a possible genetic basis for the derived feature of twinning, a finding that may be applied to better understanding of twinning in humans.

MAIN TECHNOLOGIES AND METHODS USED

- Marmoset model development
- Ultrasonography
- Open circuit respirometry
- Behavioral testing

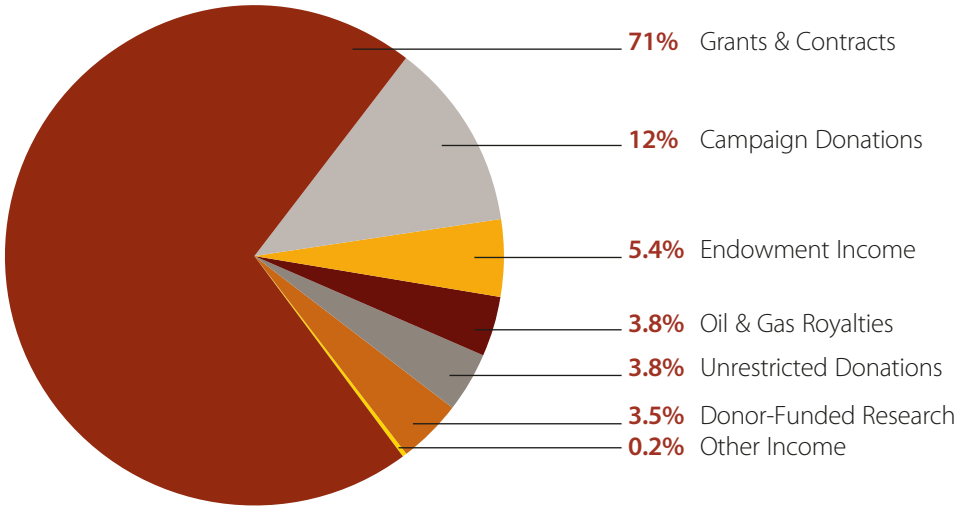
PUBLICATIONS

- **Tardif SD**, Ross C, Bergman P, Fernandez E, Javors M, Salmon A, Spross J, Strong R, Richardson A. Testing efficacy of administration of the anti-aging drug rapamycin in a non-human primate, the common marmoset. *J Gerontol Biol Sci* 2015, May; 70:577-588. PMID: 25038772, PMC4400395
- Power ML, Ross CN, Schulkin J, Ziegler TE, **Tardif SD**. Metabolic consequences of early onset of obesity in common marmoset monkeys. *Obesity* 2013, 21:E592-E598. PMC3855166
- Harris RA, **Tardif SD**, Vinar T, Wildman DE, Rutherford JN, Rogers J, Worley KC, Aagaard KM. Evolutionary genetics and implications of small size and twinning in callitrichine primates. *Proc Natl Acad Sci USA* 2014, Jan; 111:1467-1472. PMC3910650

A complete list of publications can be found at www.ncbi.nlm.nih.gov/sites/myncbi/141TjGAXrEMQK/bibliography/47791879/public/?sort=date&direction=ascending

Funding

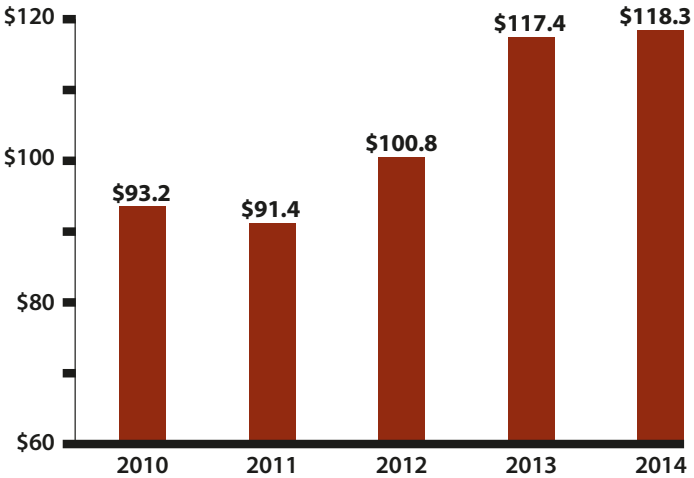
2014 Revenue*

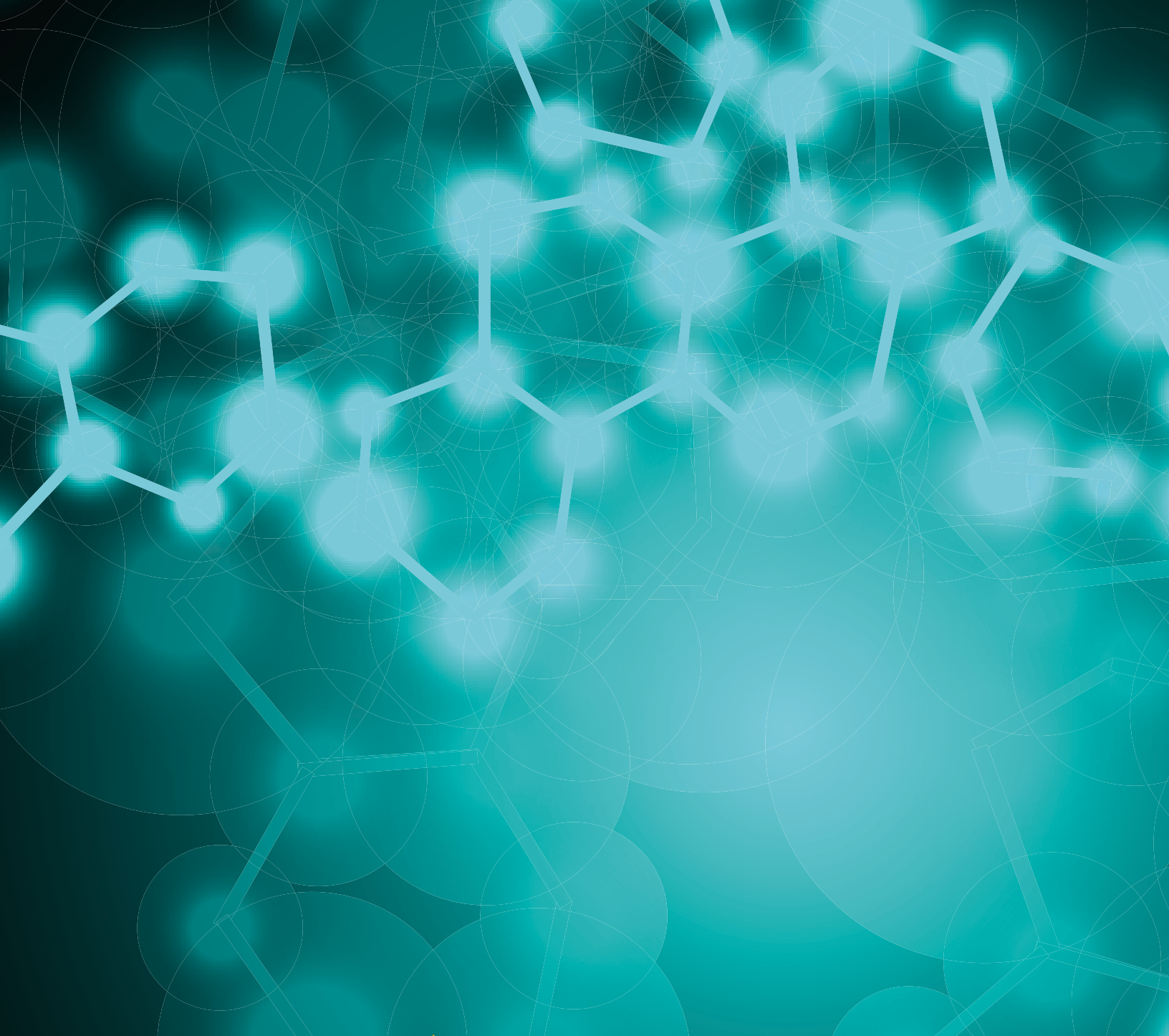


* Based on 2014 Audited Financials

Value of Endowment

In Millions of Dollars





TEXAS BIOMEDICAL
RESEARCH INSTITUTE
Enhancing lives through discovery℠

Texas Biomedical Research Institute | P.O. Box 760549 | San Antonio, TX 78245

www.txbiomed.org

210.258.9400

CREDITS

Lisa Z. Cruz, Texas Biomed Director of Public Relations, Editor

Jeffrey Heinke Design, Design

Claudia Olivier, Writer

IMAGES

Greg Harrison Photography

Texas Biomedical Research Institute archives

The Scientific Report is a publication of the Texas Biomedical Research Institute.