Scientific Report

2013–2014

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Cover: Image shows Ebolavirus (blue) infecting cells and causing clusters of autophagy proteins (green) to go to the cell surface. Cells are faintly grey and endosomes that virus uses to infect cells are red. The autophagy proteins are normally used to scavenge waste products inside the cell but here, Ebolavirus manipulates these proteins, moving them to the surface. This may prevent them from functioning, preventing virus destruction or actually help virus to infect cells.

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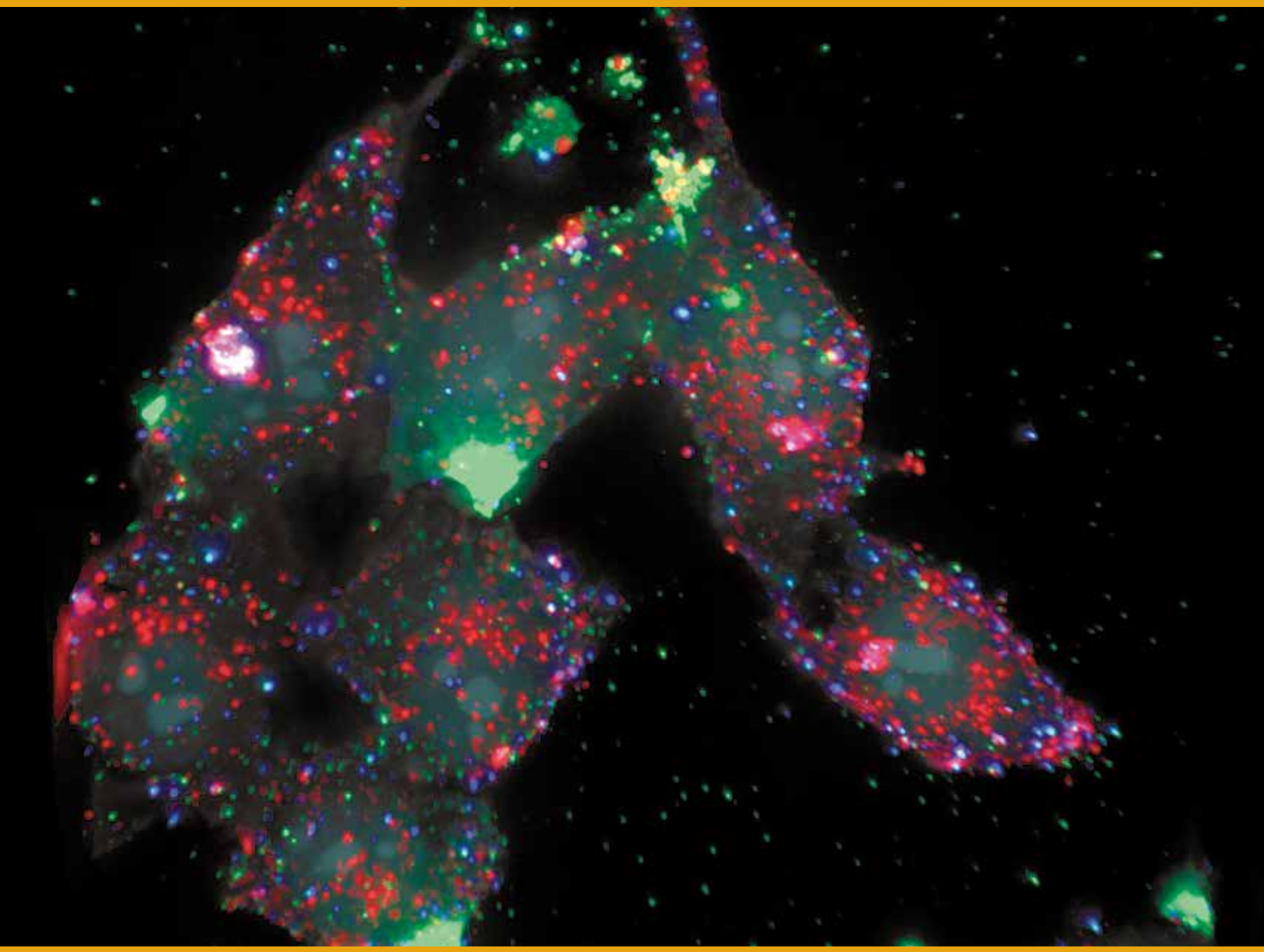

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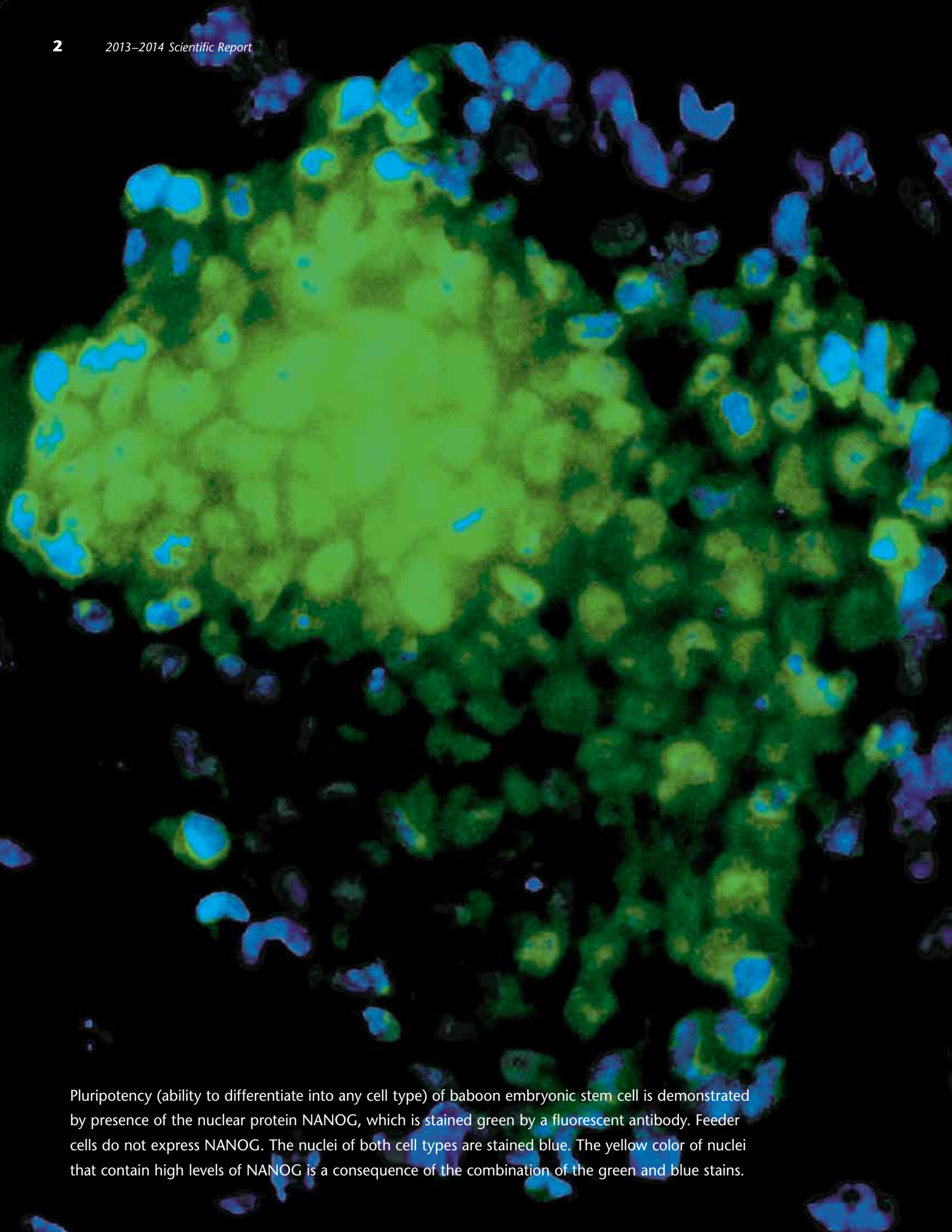


Pluripotency (ability to differentiate into any cell type) of baboon embryonic stem cell is demonstrated by presence of the nuclear protein NANOG, which is stained green by a fluorescent antibody. Feeder cells do not express NANOG. The nuclei of both cell types are stained blue. The yellow color of nuclei that contain high levels of NANOG is a consequence of the combination of the green and blue stains.

Letter from the President

Dear Colleagues and Friends,

I am very pleased to share with you the 2013-14 biennial *Scientific Report* for the Texas Biomedical Research Institute. In it, you will see that our staff continues to challenge the boundaries of scientific knowledge, seeking new understanding of the etiology of a variety of diseases and conditions — from hepatitis to diabetes to mental illnesses to heart and circulatory disease, and many others. And from this better understanding will come medical breakthroughs that improve the lives of people in the United States and all over the world.

Well before I came here, I had profound appreciation for the quality of the faculty and the divearse resources that enable new discovery. Of course, the Southwest National Primate Research Center is the most visible of these resources, but we also have numerous ongoing human population studies, biocontainment laboratories that allow our investigators to study the deadliest of pathogens, and the AT&T Genomics Computing Center, which contains 8,000 processors, making it the largest facility of its kind in the world.

We are adding to these resources by bringing on line in 2014 the Earl Slick Research Center, a 70,000-square-foot laboratory and support services building that will consolidate the Primate Center's research program, expand laboratory space for the Virology and Immunology Department and create new administrative space that will free up room to provide better adjacencies for various support services.

We have also added two new senior faculty members to our staff, Dr. Michael Olivier, a highly regarded specialist in functional genomics in the Department of Genetics, and Dr. Ruth Ruprecht, a pioneering AIDS researcher in the Department of Virology and Immunology. Each of these individuals brings new ideas and new techniques to an already vibrant intellectual climate.

I very much believe in the value of independent research institutes like ours, which are essentially single-mission organizations focused on scientific advancement. We are entrepreneurial in spirit and programmatically flexible. This is demonstrated in our recent research initiative in Parkinson's disease. While we have had an ongoing interest in neuroscience for some eight years, we had the opportunity to expand our efforts with the support of a private foundation whose founders had a strong interest in addressing the problem of Parkinson's. In just a few short months, a research plan based upon our existing strengths in brain research evolved into a highly promising project that could impact both the way Parkinson's is studied and how it could be better diagnosed and treated.

These are not easy times for the research community because of severe fiscal constraints at the federal level. Texas Biomed is not exempt from these challenges. However, we are exploring new relationships with industry as well as creative ways of identifying new sources of philanthropic support.

". . . Our staff continues to challenge the boundaries of scientific knowledge, seeking new understanding of the etiology of a variety of diseases and conditions – from hepatitis to diabetes to mental illnesses to heart and circulatory disease, and many others. And from this better understanding will come medical breakthroughs that improve the lives of people in the United States and all over the world."

This is too exciting a time in science to retrench. We must seize opportunities as we find them, all in order to extend the boundaries of our knowledge to benefit the health of existing and future generations. We greatly appreciate your interest and support, and look forward to working with you to mitigate, and eventually eliminate, life-changing and life-threatening illnesses.

Kenneth P. Trevett, J.D.
San Antonio, TX, 2014

Letter from the Chief Scientific Officer

Great science depends on the collaborative interactions of talented scientists, novel ideas and the resources to bring those ideas to fruition. Scientists at the Texas Biomedical Research Institute have an extraordinary record in all three of these areas. In the pages of this Scientific Report are descriptions of the work of our faculty members, their accomplishments and plans for the future. While these are summaries of exciting science, none of the research programs would be possible without the foresight and generosity of our Board of Trustees and the generous donors who have sustained our research enterprise since its founding in 1941.

Some recent research highlights include:

- Localization on human chromosome 18 of a major gene that influences preterm birth (*Molecular Human Reproduction* 19:687-96, 2013). The gene is likely to be plasminogen activator inhibitor-2, which is active in the placenta. Understanding genetic influences on preterm birth may enable susceptible women to be identified and interventions to be developed.
- Localization on baboon chromosome 11 of a cluster of genes that influence plasma LDL cholesterol levels when the animals are fed a high-fat diet (*Journal of Lipid Research* 54:1776-85, 2013). Understanding genetic influences may lead to new strategies for preventing elevation of plasma LDL cholesterol levels in susceptible individuals.
- Demonstration that a novel hepatitis B anti-viral drug induces prolonged suppression of hepatitis B virus in chronically infected chimpanzees (*Gastroenterology* 144:1508-17, 2013). This is the first novel drug developed in more than a decade for hepatitis B, which kills 600,000 people every year.
- Demonstration in rhesus monkeys that inflammation of the gums does not enhance oral transmission of SIV, the monkey equivalent of HIV (*Journal of Virology* 87:1750, 2013). This finding indicates that oral transmission of HIV is not likely to be enhanced in people with gingivitis.
- Demonstration that baboon embryonic stem cells can completely heal an artery that has been stripped of its endothelium, the inner lining that is responsible for the function of the vessel (*Stem Cells and Development* 15:631-42, 2013). This work paves the way for developing bioengineered arteries from human stem cells for bypass operations.

These examples are just a glimpse into the work of Texas Biomed, which includes developing defenses for bioterrorism, identifying genes that influence susceptibility to complex diseases and developing vaccines for some of the world's most devastating infectious diseases.

Scientists in the Department of Virology and Immunology are contributing to the global effort to develop a better understanding of hepatitis, AIDS, tuberculosis, herpes, and Ebola and other hemorrhagic fevers, with the goal of developing better preventive and therapeutic strategies. Ruth Ruprecht, M.D., Ph.D., recruited to the department in July 2013 as Scientist and Director of the AIDS Research Program, brought $1.5 million in NIH funding for the current year to support her

research programs on the development of an AIDS vaccine and prevention of congenital transmission of HIV infection from mother to child. The opportunities and potential to capitalize on new vaccine and drug strategies against the world's greatest infectious disease killers and potential bioterrorism threats have never been better.

In the Department of Genetics, scientists are advancing human health by characterizing the genetic components of susceptibility to complex diseases of public health importance in order to identify new drug targets for treatment and to develop novel prevention strategies. Ongoing research efforts are focused on the influence of genetic and environmental factors on heart disease, obesity, diabetes, mental illnesses, parasitic infections, osteoarthritis and osteoporosis. The department's population genetic studies of complex diseases are conducted with a variety of U.S. populations, including Mexican Americans, American Indians and Alaskan Natives, as well as with defined populations in developing countries, including Brazil and Nepal, among others. Michael Olivier, Ph.D., recruited to the department in July 2013 as a Scientist, brought a $2.6 million NIH grant for the support of a national Center of Excellence in Genomic Science. His mass spectrometry laboratory brings new capabilities in determining how genes contribute to health and disease states.

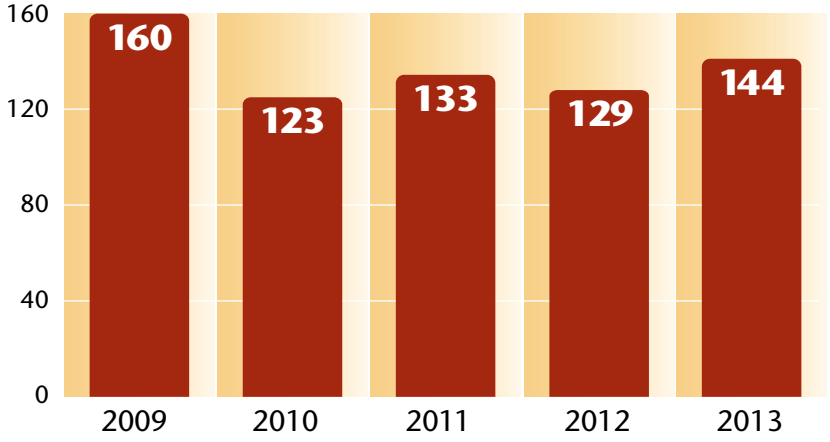
While many of the research projects based in the two Texas Biomed departments are collaborations with the Southwest National Primate Research Center, scientists based in the primate center also have leadership roles in conducting research on cardiovascular disease and on the effects of maternal nutrition on fetal development in the pedigreed baboons; in testing drugs in baboons and other monkey species to treat Chagas disease, which is a potentially lethal parasitic disease that affects 10 million to 12 million people in Latin America; in developing a new vaccine for tuberculosis using rhesus monkeys; and in conducting research in cholesterol metabolism, nonalcoholic fatty liver disease, and melanoma using the Texas Biomed laboratory opossum colony.

Much of the science discussed above would not be possible without our extraordinary resources. The biosafety level 4 maximum containment laboratory, which is crucial in support of the nation's biodefense efforts,

Texas Biomed Research Grant and Contract Funding in 2011
(millions of dollars)

	Continuing and New Awards, 1-Year Period	New Awards, Entire Project Period
Federal, Commercial & Miscellaneous		
Genetics	$14.4	$15.4
Virology & Immunology	9.5	11.1
SNPRC	8.9	0.9
Subtotal	32.8	27.4
Philanthropic	1.7	2.6
Total	**$34.5**	**$30.0**

Number of Texas Biomed Publications by Year



allows our scientists to safely study lethal pathogens for which there are no known treatments or cures. The AT&T Genomics Computing Center houses 8,000 processors working in parallel to crunch out the data necessary to discover disease-influencing genes. The Southwest National Primate Research Center is home to 2,500 nonhuman primates. More than 900 baboons in the pedigreed colony have been genotyped, and that information has been used to create a baboon genetic linkage map, the first gene map of any nonhuman primate. Together, the pedigreed colony and the baboon gene map give scientists an incredibly powerful research tool for finding the genes that underlie natural susceptibility to, or protection from, a variety of diseases.

Major new multiyear grants awarded during 2013 provide an infusion of funding that will enhance our opportunities to contribute to solving a broad range of public health problems. In addition to the awards brought by Dr. Ruprecht, the Department of Virology and Immunology received $9.6 million in multiyear awards, primarily for research on vaccines against hemorrhagic fever and other lethal viral diseases.

In addition to the award brought by Dr. Olivier, the Department of Genetics was awarded new grants of $3 million for research on cardiovascular disease, $2.7 million for research on diabetes, $1.8 million to identify genes that affect salt-sensitive hypertension and $1 million for research on osteoporosis.

These new grants and the extraordinary Texas Biomed resources, together with talented investigators and great ideas, will enable us to continue to pursue new diagnostic, preventive and therapeutic strategies for a wide range of infectious and complex diseases. The discoveries made by our scientists are contributing to a healthier world.

John L. VandeBerg, Ph.D.
Chief Scientific Officer

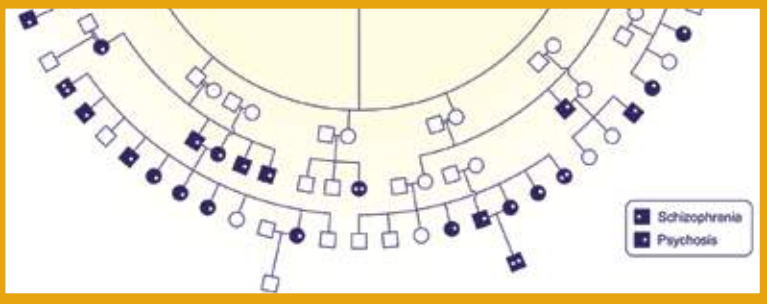
Table of Contents

Department of Genetics

Texas Biomed's Department of Genetics works to advance human health through basic biomedical research with animal and human populations, specifically by characterizing the genetic components of susceptibility to common complex diseases of public health importance. Once the individual genes influencing a given disease are known, this genetic information can be used in drug development efforts to find more effective cures or methods of prevention of disease. The information can also be used to target available drugs and other types of interventions to those individuals most likely to develop disease. Ongoing research efforts are focused on the influence of genetic and environmental factors on heart disease, obesity, diabetes, psychiatric disease, parasitic infections and osteoporosis. Scientists are also undertaking important work on the single-gene disorder cystinosis. The discoveries generated by departmental scientists were reported in 184 papers published in 2012 and 2013.

Over the past five years, Texas Biomed's geneticists have generated more than $93 million in total funding. The projects are extremely diverse, covering a range of topics from metabolic disease through parasitic disease and a number of approaches from statistical genetics to molecular biology. During 2013 major new awards supported work on a variety of health issues and genetic approaches. For example, Laura Almasy, Ph.D., a genetic epidemiologist, received a $2.5 million grant award from the National Institute for General Medical Sciences of the NIH to support the continuation of the Genetic Analysis Workshops through their 32nd year of operations. These workshops provide a testing ground for newly developed statistical genetic methods, and they have a huge impact on the field. Statistical geneticist Harald Göring, Ph.D., received a $2.7 million grant to support his research on blood metabolites and their relationship to risk for developing diabetes, a study that builds on the scientific infrastructure developed over the last 20 years in the San Antonio Family Studies. To support her new project on the discovery of genetic variants and mechanisms that underlie salt-sensitive hypertension, molecular geneticist Laura Cox, Ph.D., generated a $1.8 million grant from the National Heart, Lung, and Blood Institute. Shelley Cole, also a molecular geneticist, received a major grant totaling $2.9 million in funding to support a genetics center for the Strong Heart Study, a study of cardiovascular disease in Native Americans in which she has been involved for many years. Departmental scientists have reported the results of genetic studies in humans, nonhuman primates and parasitic organisms in about 100 papers published each year in the scientific literature. The high-impact discoveries published in the past two years included:

- Localization of a major genome region influencing artemisinin resistance in malaria (Ian Cheeseman, Ph.D., Tim Anderson, Ph.D., and colleagues);
- Identification of a gene influencing risk for depression (John Blangero, Ph.D., Joanne Curran, Ph.D., and colleagues);
- The first localization of a gene influencing preterm birth (Geetha Chittoor, Ph.D., Ravi Duggirala, Ph.D., and their collaborators);
- A study of the genetic factors influencing aging of the brain led by Blangero; and
- The localization of genetic factors influencing Epstein-Barr virus infection (Rohina Rubicz, Ph.D., Harald Göring, Ph.D., and colleagues).



"Using the state-of-the-art resources of the AT&T Genomics Computing Center, our team focuses on statistical genetic methodology, developing and applying the tools that scientists use to identify and characterize genes influencing common, complex disorders and related risk factors."

Laura A. Almasy, Ph.D.

Scientist, Genetics

Almasy's research examines the role that genes play in complex conditions like heart disease and neurological and psychiatric conditions. With grants from the National Institutes of Health, her group is examining genetic influences on cardiovascular disease and schizophrenia. She also collaborates on studies seeking to localize genes influencing normal variation in brain structure and function, alcoholism and other types of addiction.

Many of her studies focus on quantitative risk factors related to psychiatric disorders. In collaboration with colleagues at the University of Pennsylvania and University of Pittsburgh, Almasy is studying genetic influences on cognitive function in individuals with schizophrenia and their family members. Disordered cognition is a hallmark of schizophrenia and affected individuals perform poorly on a variety of cognitive tests. However, unaffected first-degree relatives of individuals with schizophrenia also perform worse than average, suggesting that these measures are a reflection of underlying vulnerability to schizophrenia rather than an outcome of the disorder. Recently, structural and functional brain imaging and genome-wide measures of both DNA methylation and mRNA levels have been added to the study, providing layers of genetic data at both the gene sequence and gene expression levels and phenotypic data covering brain structure and function, behavior and diagnosis.

Almasy also leads the Genetic Analysis Workshop, a biennial competition described as "a giant soap box derby" among statistical geneticists to devise and test methods for localizing genes and genetic variants influencing human disease. The workshop, started by Texas Biomed Senior Scientist Emeritus Jean MacCluer in 1982, is funded by the NIH and typically draws 100 or more entries from teams around the globe. Many of the genetic analysis methods currently in use debuted at the workshop. Genetic Analysis Workshop 18, held in 2012, focused on methods for analyzing human whole genome sequence data and methods for genetic analysis of longitudinal data. Planning is now underway for Genetic Analysis Workshop 19, to be held in the fall of 2014.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=55**

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Staff

Left to right: Mark Kos, Laura Almasy, Ellen Quillen

"Our primary aim is to identify the genes that underlie drug resistance in the malaria parasite (Plasmodium falciparum) *and the parasitic fluke,* Schistosoma mansoni. *Identification of these genes will allow us to monitor resistance spread in the field, to redesign drugs to restore efficacy and to better understand the dynamics of resistance evolution.*

Timothy J. C. Anderson, Ph.D.

Scientist, Genetics

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 organizations such as the Bill and Melinda Gates Foundation have generated new hope of controlling or even eliminating these diseases. Our laboratory focuses on two of the most important human parasites — malaria, caused by the protozoan Plasmodium falciparum, and Schistosomiasis, caused by the blood fluke in the genus *Schistosoma*.

Malaria infects around 500 million people each year, killing 1.7 million-2.5 million people. There is currently no vaccine and resistance to all five classes of antimalarial drugs has now been reported. We are using three different strategies to identify genes that underlie resistance. First, we are using genome-wide association methods to systematically search for the genes involved. As the malaria genome is relatively small, we can use whole genome sequence information from populations of parasites to achieve this goal. Second, we are examining the role of copy number variation — already this approach has characterized an important gene involved in drug resistance. Finally, we are selecting resistant parasites in the laboratory and using next-generation sequencing methods to identify the genetic changes that have occurred. Our work involves collaborators in South America, Africa and Southeast Asia.

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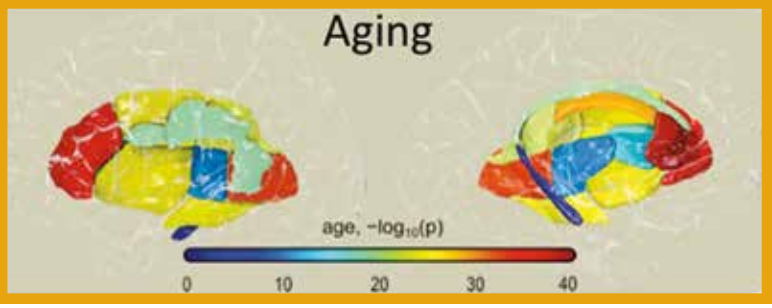
Schistosomiasis is caused by blood flukes (*Schistosoma* spp.). These parasites infect over 270 million people in Africa, South America and Asia, and utilize snail intermediate hosts. The adult worms live in the blood vessels, but the eggs cause pathology by lodging in the liver or intestine wall, where granulomas form, resulting in periportal fibrosis and hepatosplenic disease. Our work with schistosomes uses a different approach to genetic mapping. We have conducted genetic crosses in the laboratory to generate the first genetic map for a human helminth parasite. We are now exploiting this map together with exome sequencing to identify genes that underlie oxamniquine and praziquantel resistance and other biomedically important traits such as host specificity. Our schistosome research involves collaborators in San Antonio (University of Texas Health Science Center), Italy and the UK.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=4**

Staff

Left to right: Marina McDew-White, Fatma Bilgiç, Tim Anderson, Ian Cheeseman, Winka Le Clec'h, Shalini Nair, Frédéric Chevalier



"Cutting-edge deep sequencing techniques are enabling us to more quickly find gene variants and measure their output, speeding the pace of translational research that leads to better diagnostics and treatments. We are definitely moving to where theory meets practice."

John Blangero, Ph.D.

Scientist, Genetics

Theory is meeting practice at the AT&T Genomics Computing Center, where Blangero directs the "computer ranch," a cluster of 8,000 processors that make Texas Biomed one of the most powerful genetic analysis centers in the world. Blangero and his research team are recognized as pioneers and global leaders in the field of statistical genetics, for which they have developed and maintained a software package that is used all over the world to perform complex genetic analyses. Texas Biomed's computing power, coupled with latest advances in gene sequencing technology, have allowed Blangero and his team to undertake whole genome sequencing and high throughput deep-sequencing, which promise to bring clarity to many mysteries of human disease.

Philanthropic funding is playing an increasingly significant role in research projects at Texas Biomed. Grants from private foundations have enabled Blangero and colleagues to begin bold new inquiries into the genetic underpinnings of Parkinson's disease and multiple sclerosis. This new work builds on the resource of the San Antonio Family Studies, a 22-year-old partnership with the Mexican American community of San Antonio. Blangero directs the project, which has assembled data from about 2,000 individuals from 50 extended Mexican American families into a resource that has brought insight into the inherited nature of complex diseases like diabetes and heart disease. In this newest project, scientists will study the genes of several individuals who have developed Parkinson's disease or multiple sclerosis, along with some of their close relatives. Blangero and colleagues hope to gain broad knowledge on the interaction of genetic and environmental factors in these disorders. This work could lay the foundation for improved therapies and lead to biomarkers that can identify people at-risk for multiple sclerosis and Parkinson's disease.

Work continues with San Antonio's Mexican American research volunteers on a six-year-old project to understand the role of genes in the developing and functioning brain. Blangero and his co-investigator, David Glahn, Ph.D., of Yale University, recently received funding to recruit 500 more individuals for this study, called the Genetics of Brain Structure and Function, or GOBS. The study already has led to important results. Late in 2013, a study published in the journal *Proceedings of the National Academy of Sciences*, demonstrated profound aging effects on neurocognitive decline and declining white matter integrity. Scientists showed that the traits were heritable and they identified different sets of genes that were responsible for the two biological aging processes.

Blangero's team has expanded an ongoing collaboration with the pharmaceutical company Eli Lilly. Geneticists are working with the drug manufacturer to identify novel drug targets for the treatment of cardiovascular disease and to test existing medications for their potential uses on a variety of genetic targets.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=14**

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Staff

Left to right: Mario Almeida, Jeff Williams, Juan Peralta, Vince Diego, Hemant Kulkarni, Gerry Vest, Manju Mamtani, Jack Kent Jr., Michael Proffitt, Charles Peterson, Katy Freed, Satish Kumar, John Blangero

"The focus of our work is in identifying epigenetic events that contribute to the development of complex diseases. By merging findings from both genetic and epigenetic studies, we hope to better delineate the biological mechanisms that drive the development of psychiatric disorders, heart disease and cancer, thus identifying novel targets for drug development."

Melanie Carless, Ph.D.

Associate Scientist, Genetics

Over the past few years, genetic studies have begun to unravel the biological mechanisms that drive complex disease development, although there are still many gaps in our knowledge of these processes. Epigenetic mechanisms, such as DNA methylation and microRNA regulation, are now being seen as significant players contributing to the development of complex diseases, although how these factors integrate with our genetic architecture is not well understood. Carless's research focuses on identifying epigenetic variation that contributes to the development of various complex diseases and how these changes might influence and interact with genetic variation to propel disease progression.

Carless is investigating how changes in microRNA expression influence variation in neuroanatomical and neurocognitive endophenotypes, and how this variation might play a role in psychiatric disorders such as depression, bipolar disorder and schizophrenia. Recently, Carless's laboratory has identified several microRNAs whose expressions are both heritable and appear to influence neurological traits associated with depression. In addition, Carless and her colleagues have been investigating changes in DNA methylation levels that might influence traits associated with metabolic syndrome. She has identified a number of genes that show changes in DNA methylation levels that are strongly associated with type 2 diabetes and which have not been implicated by more traditional genetic analyses.

Carless believes that it is essential to gain a better understanding of both genetic and epigenetic factors driving the development and progression of mental disorders, heart disease and cancer in order to identify appropriate biological targets for better therapeutic intervention. Recent advances in the field have resulted in the development of therapeutics that specifically target methylation and microRNA expression. It is hoped that the reversal of deleterious changes will lead to a return of normal genetic regulation. Carless plans to integrate her findings into *in vitro* models by establishing protocols for the generation of neurological cell lines from the blood of patients with psychiatric disorders. Her work aims to advance the current knowledge of epigenetic involvement in complex diseases and determine interactions that influence genetic regulation to identify novel targets for drug development.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=128**

Publications

- **Carless MA**, Glahn DC, Johnson MP, Curran JE, Bozaoglu K, Dyer T, Winkler A, Cole S, Almasy L, MacCluer J, Duggirala R, Moses E, Göring HHH, Blangero J (2011) Impact of DISC1 variation on neuroanatomical and neurocognitive phenotypes. *Mol Psychiatry* 16(11): 1096-104.
- Kulkarni H, Göring HHH, Diego V, Cole S, Walder KR, Collier GR, Blangero J, **Carless MA** (2012) Association of differential gene expression with imatinib and omacetaxine toxicity in lymphoblastoid cell lines. *BMC Medical Genomics* 5:37.
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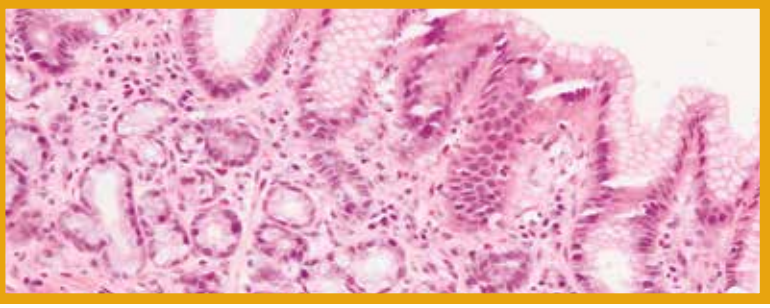
Staff

Left to right: Jessica Valdez, Kara Peterson, Marcelo Leandro, Melanie Carless, Hemant Kulkarni, Jennifer Neary



"Increasingly we are looking at a broader spectrum of complex diseases associated with obesity. We can't just study obesity; we have to look at the related metabolic pathways, which in turn affect diabetes, heart disease, kidney function, even the brain. They all are interconnected. That is the real distilling point. None of these things are separable. While you may be focused primarily on diabetes, obesity or heart disease, there are underlying connections among all of these. To work in one at the exclusion of the others is naïve."

Anthony G. Comuzzie, Ph.D.

Scientist, Genetics

A recognized authority in the genetics of obesity, Comuzzie continues to investigate the complex picture of how genetics and diet influence a wide array of medical issues including diabetes, heart disease, brain functioning and even prenatal development.

Several years ago, his lab developed and tested a "challenge" diet for baboons that duplicated the fat, sugar, salt and caloric content of the typical fast food meal that is the mainstay of so many Americans' diets. His pilot studies demonstrated how the combination of fat and sugar, especially, accelerated development of obesity and metabolic dysfunction in this research model for human atherosclerosis and diabetes. Since then, Comuzzie's lab joined with researchers around the world who are adapting this diet for use with other nonhuman primate models in the study of prenatal development, diabetes, cardiovascular disease and cancer risk.

With its recent investments in state-of-the-art gene sequencers, upgraded computer firepower and well-characterized family study populations, Texas Biomed scientists have unparalleled resources for investigating heritable factors that influence obesity and comorbidities. Comuzzie and other scientists have generated more than 1 million SNP typings and a genome-wide association study, and have begun to analyze calorimetry data from 1,400 participants in the Viva La Familia study. Collectively, this information is generating new findings about novel genes that influence the energy expenditure rates in cells.

From a genetics standpoint, energy expenditure has been largely understudied 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. Texas Biomed's unique resources enable Comuzzie and his team to make important findings.

Publications

- Cox LA, **Comuzzie AG**, Havill LM, Karere GM, Spradling KD, Mahaney MC, Nathanielsz PW, Nicolella DP, Shade RE, Voruganti S, Vandeberg JL (2013) Baboons as a model to study genetics and epigenetics of human disease. *ILAR J* 54:106-21.
- Fabbrini E, Higgins PB, Magkos F, Bastarrachea RA, Voruganti VS, **Comuzzie AG**, Shade RE, Gastaldelli A, Horton JD, Omodei D, Patterson BW, Klein S (2013) Metabolic response to high-carbohydrate and low-carbohydrate meals in a nonhuman primate model. *Am J Physiol Endocrinol Metab* 304:E444-51.
- Higgins PB, Rodriguez PJ, Voruganti VS, Mattern V, Bastarrachea RA, Rice K, Raabe T, **Comuzzie AG** (2013) Body composition and cardiometabolic disease risk factors in captive baboons (Papio hamadryas sp.): Sexual dimorphism. *Am J Phys Anthropol* 153:9-14.
- Hohenadel MG, Thearle MS, Grice BA, Huang H, Dai MH, Tao YX, Hunter LA, Palaguachi GI, Mou Z, Kim RC, Tsang MM, Haack K, Voruganti VS, Cole SA, Butte NF, **Comuzzie AG**, Muller YL, Baier LJ, Krakoff J, Knowler WC, Yanovski JA, Han JC (2013) Brain-derived neurotrophic factor in human subjects with function-altering melanocortin-4 receptor variants. *Int J Obes* (Lond) [Epub ahead of print]
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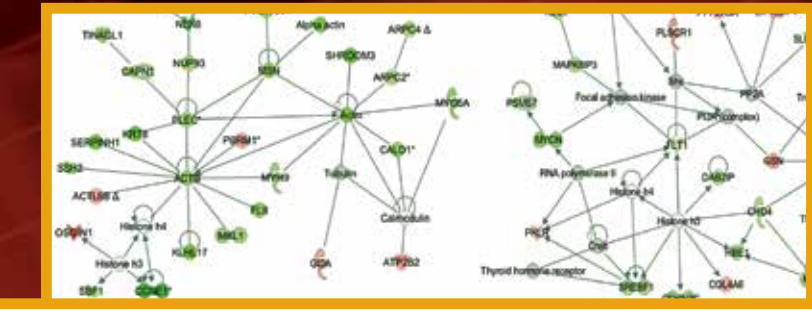
Comuzzie's research also recently developed new information about the melanocortin 4 receptor gene that previously was linked to rare but heritable cases of extreme obesity. Analysis of the Viva La Familia family study data has identified other variants of the same gene that are more common and that cause more moderate effects in a greater number of people. Comuzzie has shown that this gene is a significant player in the problem of obesity. Some of the variants are rare but have a major effect, while others are more common and have a more modest effect.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=58**

Staff

Left to right: Sandy Laston, Anthony Comuzzie, Vicki Mattern, Saroja Voruganti

Not shown: Raul Bastarrachea



"Research by multiple investigators indicates that entire transcriptional networks play roles in genetic responses to environmental challenges. Our goal is to identify network responses to dietary fat that differ in individuals with good cholesterol profiles versus bad cholesterol profiles. In addition, we are studying the role of the maternal nutritional environment on offspring health. Identification and understanding of the mechanisms by which these networks are regulated will provide RNA-based therapeutic targets for prevention of atherosclerosis."

Laura A. Cox, Ph.D.

Scientist, Genetics

The focus of Cox's research is the identification and characterization of genes involved with development of cardiovascular disease. The goal of these studies is to identify genetic and epigenetic variation in response to diet and in response to the maternal environment that influences the atherosclerotic process. Her team identified molecular genetic mechanisms by which variation in one gene influences variation in HDL-cholesterol. In addition, they have identified four novel genes that may regulate variation in LDL cholesterol. Her research team is now investigating the role of these four genes in LDL cholesterol metabolism. In addition, they are studying genes and gene variants that regulate blood pressure in response to dietary salt. Each genetic network and gene variant that is identified will provide potential therapeutic targets for modulation of blood pressure and serum cholesterol.

Cox's research team is also studying genetic and epigenetic responses to the maternal environment and the impact on offspring health with the long-term goal of determining how the maternal environment influences adult risk of heart disease. Her recent publications show that male fetuses are more dramatically impacted by maternal nutritional deficiency than female fetuses, suggesting greater health impacts on men than women.

Publications

- Karere GM, Glenn JP, VandeBerg JL, **Cox LA** (2012) Differential microRNA response to a high-cholesterol, high-fat diet in livers of low and high LDL-C baboons. *BMC Genomics* Jul 18;13:320.
- **Cox LA**, Comuzzie AG, Havill LM, Karere GM, Spradling KD, Mahaney MC, Nathanielsz PW, Nicolella DP, Shade RE, Voruganti S, VandeBerg JL (2013) Baboons as a model to study genetics and epigenetics of human disease. *ILAR J* Jan;54(2):106-21.
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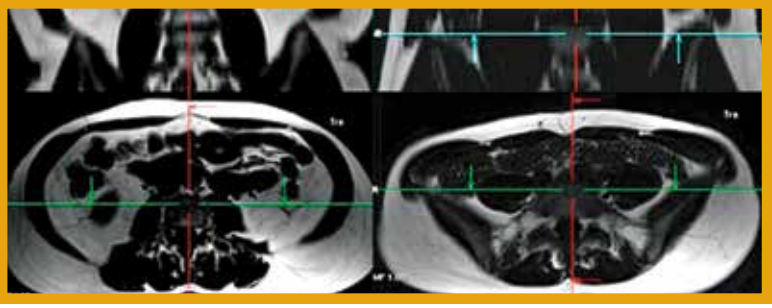
By understanding these processes and the effects on adult offspring health, specific interventions can be developed to improve maternal health during pregnancy.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=35**

Staff

Left to right: Shifra Birnbaum, Genesio Karere, Jeremy Glenn, Clint Christensen, Laura Cox, Tursun Nuermaimaiti, Kimberly Spradling-Reeves, Kenneth Lange



"Our research focuses on the identification and characterization of genes involved in complex diseases. We have been successful in the identification of several genes influencing complex phenotypes such as inflammation, diabetes and heart disease."

Joanne E. Curran, Ph.D.

Associate Scientist, Genetics

Curran's research focuses on dissecting diseases such as type 2 diabetes, obesity and cardiovascular disease in the general population to gain an insight into the biological pathways involved in disease pathogenesis.

Using a combination of next-generation sequencing and the large extended pedigrees from the San Antonio Family Study (SAFS) cohort, Curran and colleagues are identifying functional variants influencing complex diseases. As part of an NIH-funded Type 2 Diabetes Consortium, they now have whole genome sequence data on a thousand SAFS members. An independent NIH award secured by Curran and John Blangero, Ph.D., has allowed them to extend this vital whole genome sequencing collection project to an additional 1,000 participants. Additionally, exome sequencing (capturing the core 'functional' or coding regions of the genome) is available on many of the remaining SAFS participants through other projects led by Curran and colleagues in partnership with the pharmaceutical industry. This family-based genome sequencing resource is one of the most powerful datasets of its kind and will lead to the rapid identification of novel drug and diagnostic targets as it provides valuable insights into disease pathways and the biology underlying disease susceptibility and progression.

Curran has recently used her experience in cardiovascular and obesity related complex disease genomics and her collaborations with some of the leaders in the biomedical field to assess 'lipidomics' — the measurement of complex lipid profiles made up of hundreds of different fat-based molecules within the body — and further enhance the lipid disease research at Texas Biomed. The lipidomics studies add extensive value to the already complex precollected data from SAFS and allow her research to more directly interrogate the action of genes and their involvement in disease processes. This cutting edge and exciting research has already been the subject of multiple invited talks and several new manuscripts.

Expanding on industry partnerships, Curran has recently been successful in obtaining a research award to investigate miRNAs (a relatively new and potentially extremely important part of gene regulation) in plasma for the identification of novel biomarkers for cardiometabolic disease.

Publications

- **Curran JE**, McKay DR, Winkler AM, Olvera RL, Carless MA, Dyer TD, Kent Jr JW, Kochunov P, Sprooten E, Knowles EE, Comuzzie AG, Fox PT, Almasy L, Duggirala R, Blangero J, Glahn DC (2013) Identification of pleiotropic genetic effects on obesity and brain anatomy. *Hum Hered* 75(2-4):136-43.
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- Kulkarni H, Meikle PJ, Mamtani M, Weir JM, Barlow CK, Jowett JB, Bellis C, Dyer TD, Johnson MP, Rainwater DL, Almasy L, Mahaney MC, Comuzzie AG, Blangero J, **Curran JE** (2013) Variability in associations of phosphatidylcholines with metabolic syndrome in Mexican American families. *Lipids* 48(5):497-503.
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Curran is also launching a breast cancer genetics program at Texas Biomed. This represents a new and exciting area of research at Texas Biomed and a field in which her datasets and methodologies have the potential to make a significant impact on the field. Her initial studies will investigate breast density, the most significant risk factor for breast cancer development, by MRI in the Mexican American population.

Other research interests include the mitochondrial genome and its involvement in disease risk. Curran also collaborates with other scientists on metabolic syndrome in adolescents, the effect of early growth patterns on obesity and the identification of genes influencing the development of heart disease, diabetes, prediabetes, Parkinson's disease, depression, psychosis and schizophrenia.

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Staff

Left to right: Steven Howard, Lilliana Paredes, Grace Ann Arya, Katherine Truax, Joanne Curran, Ram Upadhayay, Claire Bellis

"Genetics, culture and other environmental factors interact to influence human health and disease. Using state-of-the-science molecular genetic and statistical genetic tools including most advanced sequencing technologies, our goals are to find the genes that increase our susceptibility to complex diseases such as obesity, type 2 diabetes, gallbladder disease, and metabolic syndrome and to investigate how those genetic influences are altered by the changing environment, including socioeconomic and lifestyle factors."

Ravindranath Duggirala, Ph.D.

Scientist, Genetics

With dual interests in anthropological genetics and genetic epidemiology, Duggirala's research group pursues a wide breadth of scientific inquiries among various human populations around the world. Past, present and future collaborative projects include research investigations such as genetic and cultural influences on lipids among Mennonites in Kansas and Nebraska; localization and identification of genes that influence susceptibility to complex diseases such as obesity, type 2 diabetes (T2DM), metabolic syndrome (MS), cardiovascular disease, diabetic nephropathy, and gallbladder disease (GBD) and their related quantitative traits in Mexican Americans in Texas; genetic studies of T2DM in native populations in his homeland of India; and genetic studies of tuberculosis in Mexican populations in Chihuahua, Mexico.

Duggirala and colleagues direct a variety of projects that are designed to examine genetics of complex diseases/phenotypes in adults and children. For example, they are currently involved in a major international collaborative effort (T2D-GENES Consortium) to identify the T2DM susceptibility variants, both rare and common, using whole genome sequence data obtained from selected participants of two San Antonio Mexican American (MA) family studies and whole exome sequence data obtained from the unrelated case/control data sets from various ethnic groups including MAs from San Antonio. Besides the ongoing GBD susceptibility gene discovery activities, other genetic studies performed recently include localization of a major locus for premature birth and some major loci that have potential common genetic influences on birth weight and MS-related traits. Given the burden of childhood obesity and its risk factors, Duggirala and his team conducted the SAFARI study to examine cardiometabolic risk factors in MA children and adolescents and to examine their genetic basis. This study revealed a disturbingly high risk of overweight/obesity, MS and prediabetes, and several of the examined traits exhibited strong genetic influences. Their pilot study conducted to identify risk factors associated with progression from latent tuberculosis (TB) infection to TB in Mexicans showed that TB was associated with poor nutrition, T2DM, family history of TB, and non-Chihuahua state of birth.

Publications

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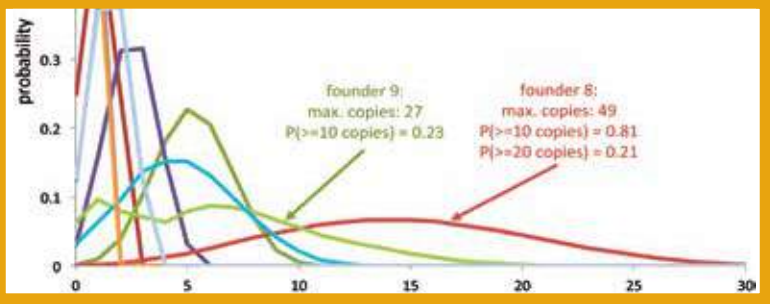
- Chittoor G, Farook VS, Puppala S, Fowler SP, Schneider J, Dyer TD, Cole SA, Lynch JL, Curran JE, Almasy L, MacCluer JW, Comuzzie AG, Hale DE, Ramamurthy RS, Dudley DJ, Moses EK, Arya R, Lehman DM, Jenkinson CP, Bradshaw BS, DeFronzo RA, Blangero J, **Duggirala R** (2013) Localization of a major susceptibility locus influencing preterm birth. *Mol Hum Reprod* 19:687-96.

They will continue their ongoing gene discovery studies (and their extensions in the near future) focused on T2DM, GBD, MS and its association with birth weight and premature birth, which have major public health relevance in terms of disease prevention and treatment. Since the SAFARI data warrant immediate efforts for intervention, the team is seeking external funding to conduct a 12-week long community-based, family-centered lifestyle intervention study involving SAFARI participants, and to examine genetics of differential response to lifestyle intervention. The TB pilot data have provided the necessary foundation for a potential project on the genetics of TB in Mexican populations, which is being submitted.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=64**

Staff

Left to right: Vidya Farook, Azaneth Arellanes, Valessa Agosto-Cusano, Roy Resendez, Miguel Aguilar, Ravindranath Duggirala, Amuche Ezeilo, Sobha Puppala, Geetha Chittoor



"We seek to unravel the genetic mysteries behind our human individual characteristics, such as our behaviors, skills, disease predispositions and life expectancy. Our research involves the development of sophisticated statistical and computational methods designed to identify functional genetic variants and the application of these methods to a wide variety of human conditions, including both rare and common diseases, as well as quantitative biomarkers related to disease risk."

Harald H. H. Göring, Ph.D.

Scientist, Genetics

Over the last decade, a technological revolution has taken place in molecular biology, allowing scientists to obtain detailed data on our individual genetic constitution on a scale unimaginable only a few years ago. Armed with this genomic data, scientists all over the world are now trying to identify the genetic factors underlying human diseases and other characteristics. However, the human organism, in its complexity, remains a good guardian of its many secrets. To overcome this hurdle, Göring's research group works on the development of sophisticated statistical methods and applies them to well-designed human datasets and novel "omics" data.

There are currently four main research topics in Göring's research group: They are working on a variety of statistical methods and search strategies for genes influencing risk of disease. Currently the focus is on identifying rare genetic variants with a strong individual effect on complex traits in families. Such variants are likely to be very important but are very difficult to identify. The group is taking advantage of large pedigrees of Mexican Americans from around San Antonio, with whole genome sequence data, to systematically identify functional variants influencing a variety of clinical traits and related biomarkers.

A long-time research focus is the genetic investigation of gene expression, based on the belief that many of the genetic factors influencing the risk of common diseases are subtle changes to DNA that result in alterations in the quantity, location and/or timing of gene expression. One current collaborative project involves identification of genes increasing risk for schizophrenia, by analyzing gene expression profiles of cell lines (before and after stimulation with the neurotransmitter dopamine) from individuals with and without the disease.

Publications

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- **Göring HHH** (2012) Tissue specificity of genetic regulation of gene expression. *Nat Genet* 10:1077-8.
- Rubicz R, Yolken R, Drigalenko E, Carless MA, Dyer TD, Bauman L, Melton PE, Kent JW Jr., Harley JB, Duggirala R, Curran JE, Johnson MP, Cole SA, Almasy L, Moses EC, Dhurandhar NV, Kraig E, Blangero J, Leach CT, **Göring HHH** (2013) A genome-wide integrative genomic study localizes genetic factors influencing antibodies against Epstein-Barr virus nuclear antigen 1 (EBNA-1). *PLoS Genetics* 9:e1003147.

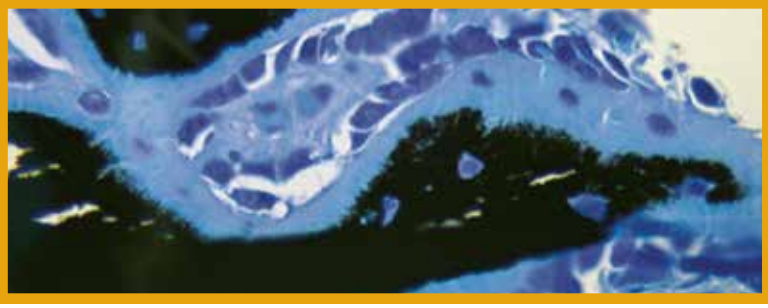
A new research project centers on metabolomics. Using a highly sensitive two-dimensional gas chromatography approach, the scientists are characterizing blood plasma from a large number of Mexican Americans. The hope is to identify early metabolic markers that can predict the risk of diabetes long before the actual onset of the disease, at which point lifestyle and other interventions may still be possible to avoid developing the disease.

Lastly, the research group has had a long interest in common infections. They have previously examined antibody titers to 13 common viral and bacterial pathogens in Mexican Americans and recently succeeded in identifying a factor located in the HLA region of chromosome 6 that influences antibody titer levels to Epstein-Barr virus, which can lead to mononucleosis and more serious diseases such as several cancers, and which may also be critical for development of lupus. They are now planning to characterize the microbiome of stool samples using DNA-based technology to assess the relationship of the microbes present to diet and a variety of health outcomes.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=57.**

Staff

Left to right: Eugene Drigalenko, Rohina Rubicz, Harald Göring, August Blackburn



"Osteoporosis (fragile bone disease) and osteoarthritis are enormous public health problems that cause significant individual suffering and rising health care costs. Osteoporosis can lead to crippling fractures. Osteoarthritis is the leading cause of disability in the U.S., and the incidence is increasing, driven by both the obesity epidemic and the overall aging of our population. With Texas Biomed's pedigreed baboon colony, its ongoing family studies, and its computing resources, my laboratory focuses on identifying the genes and biological processes that may either accelerate the risk of bone and joint deterioration or offer protection from these age-related skeletal disorders."

Lorena M. Havill, Ph.D.

Associate Scientist, Genetics

Havill and her team investigate variation in risk of two common aging-related diseases of the skeletal system — osteoporosis ("fragile bone disease") and osteoarthritis. These are extremely common age-related skeletal diseases, but their causes and, consequently, our ability to effectively prevent and treat them, remain elusive. Osteoporosis involves loss of bone from the skeleton and changes in the quality and arrangement of the remaining bone. The result is a skeleton that is more likely to fracture, especially at the hip, spine and wrist. Osteoarthritis involves destruction of the joints of the skeleton, resulting in pain, stiffness and limited mobility, which make this disease the leading cause of disability in the U.S.

Havill and her team apply molecular and statistical genetic methods in large family-based studies of baboons and humans to determine how much of the variability in risk of these diseases is caused by genes and sex differences. She uses novel, creative study designs to capture variation in traits that provide valuable information about variation in susceptibility to skeletal disease, but that have long been considered too difficult or impossible to measure. For example Havill and scientists at the Southwest Research Institute are characterizing the genetics of bone strength by measuring fracture properties of bone directly (instead of through imaging techniques) using the baboon as a research model.

In a 2013 study Havill's research with baboon bones pointed to underlying genetic differences that could explain why some people respond poorly to common anti-osteoporosis drugs and suffer atypical fractures in their femurs and osteonecrosis of the jaw.

In recent years Havill has expanded her program to conduct pioneering studies of the causes of osteoarthritis through the study of knees from baboons that died in the earliest stages of the disease. Her ultimate goal is to provide new targets for medical intervention early in osteoarthritis before significant joint destruction has occurred.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=8**

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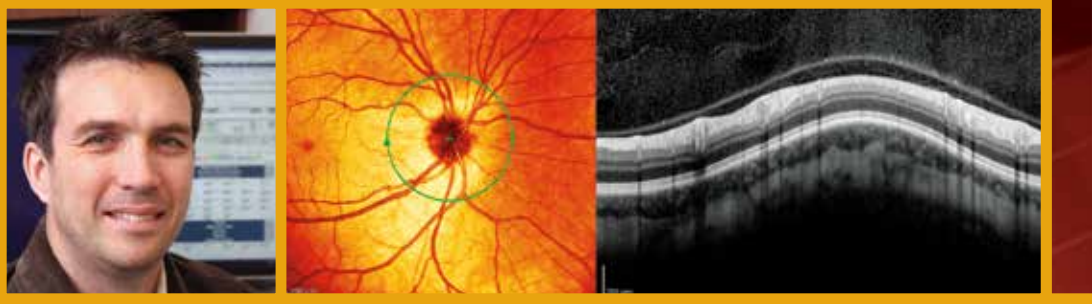
Staff

Left to right: Ahsan Choudary, Shayna M. Levine, Lorena M. Havill, Thomas Macrini, Jennifer A.K. Harris



"Visual impairment hinders our independence and quality of life. To significantly reduce its negative impact on human well-being we aim to uncover the genetic mechanisms influencing ocular health and ocular diseases of public health importance. Our discovery phase implements massively parallel sequencing and computational resources with a view to moving our discoveries 'back-to-the-bench'; our translational phase to elucidate the functional/biological characteristics of prioritized genetic variants."

Matthew P. Johnson, Ph.D.

Assistant Scientist, Genetics

Visual impairment, defined as low vision or blindness in the better-seeing eye, is a major public health concern. An aging global population and the rise of cardiovascular disease-related insults (e.g., diabetes) will only augment the negative impact visual impairment has on the individual and transition burden onto support network(s) and health care systems. Genetic mechanisms are known to influence ocular traits and major age-related ocular disorders such as cataract, glaucoma, age-related macular degeneration (AMD) and diabetic retinopathy; these disorders are progressive in nature. Johnson and his group therefore aim to decompose their genetic architecture in order to help develop/refine disease end-point therapeutics and, more importantly, objectively identify those at-risk individuals with a view to arresting the progression of these life-changing conditions.

The development of an ocular genetics research program at Texas Biomed has been boosted with pilot funding from the Max and Minnie Tomerlin Voelcker Fund. This local (San Antonio) foundation is seeding the San Antonio Family Eye Study (SAFES). SAFES' objective is to characterize the genetic mechanisms influencing the progressive nature of AMD, its end-point manifestations and other major ocular disorders in a cohort of Mexican American families within the San Antonio area. SAFES is an extension of the San Antonio Family Heart Study, an ongoing project initially conceived by Texas Biomed scientists circa 1991 to investigate the genetics of cardiovascular disease risk factors. SAFES is in collaboration with the Department of Ophthalmology, School of Medicine, UTHSCSA (Anderson K.L., co-I). Johnson is also collaborating with the Casey Eye Institute in Portland, OR (Klein M.L., PI) on an NIH-funded project to identify novel and refine existing AMD genetic susceptibility loci in a cohort of Caucasian families. This project is integrating a joint linkage/association methodology, massively parallel sequencing technology and a refined (semiquantitative) AMD phenotype to search for residual genetic liability influencing advanced AMD, and the genetic liability influencing mild-to-intermediate stages of the disease.

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Stemming from his postdoctoral work at Texas Biomed, Johnson also maintains an interest in preeclampsia, a common and serious complication of human pregnancy. Irrespective of gestational age, delivery of the fetus and placenta is the only effective means to alleviate this condition. Mothers with a history of preeclampsia and children born to a preeclamptic pregnancy are also known to be at greater risk of later-life cardiovascular disease-related ailments. Johnson continues to have an active role in a global collaboration to unmask the maternal (and paternal) molecular genetic mechanisms influencing preeclampsia susceptibility.

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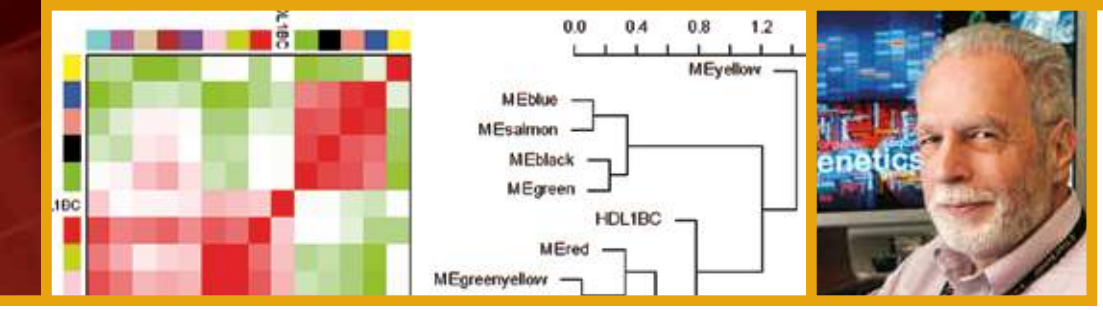
Staff

Left to right: Yvonne Garcia, Matthew Johnson



"Each human is a product of billions of reactions on multiple levels of biological organization and interactions between all the levels. Networks of interacting genes provide the blueprints for observed patterns of correlations between clinically relevant phenotypes in health and disease."

Michael C. Mahaney, Ph.D.

Scientist, Genetics

Employing statistical genetics and genomics tools, Mahaney's research exploits data on a variety of phenotypes from multiple species to address questions with implications for basic biology and biomedicine. Phenotypes studied include biomarkers of metabolic processes — such as lipid and cholesterol metabolism, inflammation, oxidative stress and cell growth — and cell structure and function. These data inform research relevant to cardiovascular diseases like atherosclerosis and stroke and age-related disorders of bone, such as osteoporosis. The work is typically comparative: Mahaney and collaborators use results from analyses of data from one species (e.g., humans, baboons, laboratory opossums, and/or mice) to generate hypotheses that they test in another to understand the genetic bases of variation in *human* health and disease.

Mahaney has long been interested in identifying genes or sets of genes that influence multiple traits (pleiotropy). This interest motivated his early work to detect pleiotropic effects of the cystic fibrosis locus on growth and development of children with that disease; later efforts to detect the effects of genes on variation in shape, size and number of teeth; and current studies to identify and understand the effects of the genes contributing to variation in susceptibility, severity and progression of common, complex disorders in humans. Although primarily analytical, his research also takes him into the field, as in a current study to identify genes influencing the structure and metabolism of bone in the people of Jiri, Nepal.

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Coordinately regulated networks of phenotypes and the genes that underlie them, are likely to be good targets for preventive and therapeutic intervention. Analyzing data from humans and baboons, Mahaney and colleagues are using multivariate statistical genetics and bioinformatics tools to reconstruct these sorts of networks. Focused mainly on cardiovascular disease risk factors, these efforts already have identified networks of genetically correlated traits that respond to different levels of cholesterol and fat in the diet of our pedigreed baboons. Mahaney and Laura Cox, Ph.D., of the Department of Genetics at Texas Biomed, also have identified networks of co-expressed genes, often hundreds (and sometimes thousands), in cells from the vascular endothelium (blood vessel wall), liver, and blood that affect variation in these responses. Similar analyses were used to identify gene co-expression networks that influence two kinds of immune-response cells that may play roles in atherosclerosis.

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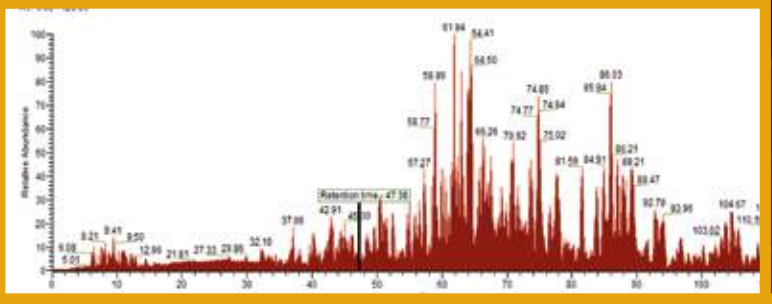

"Ongoing large-scale studies to resequence the entire genome of human patients are leading to the identification of a plethora of variants that contribute, either individually or in combination, to diseases. My laboratory has been developing and applying methods and approaches that can help in the functional analysis of these sequence variants."

Michael Olivier, Ph.D.

Scientist, Genetics

As we continue to identify changes in the genome sequence that are contributing to human diseases, the key challenge over the past few years has been how to understand what these sequence changes truly do and how they adversely affect normal genome and cell function.

For over a decade now, Olivier's group has been using an analytical approach called mass spectrometry to identify and quantify proteins in cells. Proteins mediate virtually all cell functions, and the majority of disease-associated sequence changes in the human genome are likely to adversely affect this complex protein machinery, leading to cell dysfunction and disease. By isolating and then analyzing proteins from samples from patients with specific diseases, and then comparing the findings to proteins that can be found in samples from normal control individuals, Olivier's laboratory has been trying to link changes in the DNA sequence to these changes in the complement of cellular proteins, the *proteom*.

For this effort, Olivier's group has focused on lipid abnormalities associated with human obesity and the metabolic syndrome. Patients with this disorder have higher cholesterol and plasma triglyceride levels, and their lipoprotein particles (HDL-cholesterol) tend to be smaller than normal, which is believed to contribute to the patient's risk of developing heart attacks and strokes. Patients with this abnormal lipid profile are also more likely to develop liver complications, specifically nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). In analyzing and characterizing proteins from lipoprotein particles isolated from the patient's blood, Olivier's laboratory has been working to identify specific protein changes in samples from obese patients and patients with NAFLD. These findings can then be combined with results from the analysis of gene expression in the liver of these patients and results from the analysis of DNA sequence variation to not only understand the genetic susceptibility to abnormal lipid levels and NAFLD, but also to gain insights into the underlying cellular mechanisms that contribute to this.

In addition to this ongoing work on lipid disorders, Olivier directs the Center of Excellence in Genomics Science, a collaborative project with scientists at the University of Wisconsin — Madison and the Medical College of Wisconsin supported by the National Human Genome Research Institute of the NIH. The Center is developing novel technologies to study how proteins in cells interact with the DNA and regulate the expression of genes. This ongoing effort is likely to provide another new tool that can help investigators study how DNA sequence variants in humans contribute to diseases by looking at changes in gene regulation and expression, another way in which sequence variants may alter normal cells in diseases like obesity or the metabolic syndrome.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=189**

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Staff

Left to right: Danu Sicora Perumalla, Avinash Jadhav, Michael Olivier, Prahlad Rao, Hector Guillen Ahlers

"My research program is focused on the genetic determinants of disease-related characteristics and of traits associated with normal human development. I use statistical genetic approaches and genome-wide scanning techniques to assess the genetic components of a number of parasitic diseases and of aspects of aging in normal individuals."

Sarah Williiams-Blangero, Ph.D.

Scientist and Chair, Genetics

Williams-Blangero is pursuing investigations of the genetic components underlying susceptibility to parasitic diseases in two large-scale human population studies each involving more than 2,000 participants. The soil-transmitted intestinal worm infections that affect a quarter of the world's population (hookworm, roundworm and whipworm) are the focus of a genetic epidemiological study in the Jirels of Nepal. More than 2,600 members of a single pedigree participate in the study, which to date has localized 10 genes influencing levels of helminthic infection. The second family study is based in rural Brazil and focuses on the genetic determinants of susceptibility to Chagas disease (*Trypanosoma cruzi*), the leading cause of heart disease in Latin America. Williams-Blangero is assessing the genetic components of susceptibility to infection with the parasitic cause of Chagas disease and of differential cardiac disease progression in individuals who are infected with T. cruzi. The extensive genetic characterization of the human populations involved in these studies makes them incredibly valuable for studies of other diseases and traits. For example, the Jirel population also has been the subject of research on the genetics of growth and development, dental characteristics and bone-related traits of relevance for osteoporosis. This year, Williams-Blangero and colleagues established collaborative relationships with the Tilganga Eye Institute in Kathmandu in preparation for a new study of the genetic components to eye diseases and vision in the Jirels.

Williams-Blangero also has a research program on the genetic factors influencing aging. This study builds on the unique resources of the San Antonio Family Heart Study. Utilizing the transcriptional profiles that have been generated for the members of approximately 40 large Mexican American families, Williams-Blangero and her colleagues have identified over 4,000 transcripts that are significantly correlated with chronological age. While most transcript levels show a decrease with age, 43 percent of transcripts show an increase in transcription with age.

Clearly, not all research questions can be answered by studies of humans. Nonhuman primates are critical animal models for many types of research. Through work with the Southwest National Primate Research Center (SNPRC) and the Caribbean Primate Research Center, Williams-Blangero continues to pursue an interest in genetic management of nonhuman primate colonies. She currently serves as the deputy director of the SNPRC.

▶ For more information, please visit **http://www.txbiomed.org/departments/genetics/genetics-staff-bio?u=49**

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Staff

Cheryl Raindl, Beverly French, Cindy Tumiel, Sarah Williams-Blangero, Paula Bodden, Selina Flores

Department of Virology and Immunology

The Department of Virology and Immunology develops vaccines, diagnostics and surveillance strategies, and therapeutics against viral pathogens through basic and applied research. To defeat viruses that cause AIDS, hepatitis, herpes, hemorrhagic fevers, and a host of other illnesses, departmental scientists address viruses on two different fronts. First, they examine how viruses replicate and propagate to identify their weaknesses. Second, they study how the immune system recognizes a virus and how best to stimulate immune response to clear viral infections.

A strong team is working on the development of vaccines for many potential biological weapons — known as select agents — that can cause lethal outbreaks of disease, primarily hemorrhagic fever. The team consists of Jean Patterson, Ph.D., Department Chair and Director of the Biosafety Level 4 laboratory (BSL-4); Associate Scientist Ricardo Carrion Jr., Ph.D., scientific manager of the BSL-4; Scientist Luis Giavedoni, Ph.D., immunologist; and Assistant Scientist Anthony Griffiths, Ph.D., molecular virologist. Melissa de la Garza, D.V.M., is the principal veterinarian. Together the team is working on three candidate vaccines against Ebola virus, two candidate vaccines against Marburg virus and two vaccines against Lassa Fever virus. Ebola, Marburg and Lassa viruses are particularly deadly agents that cause hemorrhagic fever.

In addition, Carrion and his team have demonstrated that two drugs currently used for treating leukemia, nilotinib and imatinib, can block Ebola replication in vitro. Furthermore, productive replication of the highly pathogenic Ebola virus Zaire strain was inhibited by c-Abl1-specific siRNAs or by the Abl-family inhibitor nilotinib by up to four orders of magnitude. These data indicate that c-Abl1 regulates budding or release of filoviruses through a mechanism involving phosphorylation of VP40. This step of the virus life cycle therefore may represent a target for antiviral therapy.

Robert Davey, Ph.D., is making great progress with the basic understanding and drug discovery of work on Ebola virus, Crimean-Congo Haemorraghic Fever Virus and Junin virus. He and his team are testing drug candidates in the high containment lab, and new compounds are coming along every day. Their work with the University of Texas at Austin and Luminex promises to make new breakthroughs in the diagnostic assays for these viruses.

Scientist Robert Lanford, Ph.D., continues to examine new therapies to treat chronic hepatitis C virus infections using the chimpanzee model of HCV. Several antiviral cocktails have been developed that cure more than 95 percent of patients in only 12 weeks. Lanford has developed a baboon model of liver cancer by genetically engineering liver cells in the laboratory.

Giavedoni collaborates heavily with the filovirus vaccine programs here. He also continues his work on the pathogenesis of HIV/AIDS utilizing nonhuman primates. In addition, Giavedoni and colleagues continued to work on projects in AIDS vaccine development and pathogenesis using the rhesus macaque/simian immunodeficiency virus (SIV) model. One project involved the use of biodegradable nanoparticles carrying small nucleic acids designed to bind and inactivate the viral genome within infected cells; studies in SIV-infected monkeys showed that these particles can transiently reduce virus in circulation.

Associate Scientist Andrew Hayhurst, Ph.D., explores the potential of a new antibody pipeline system invented to quickly respond to biothreats with a stop-gap assay. Proof of principle experiments on model antibodies and antigens have been successful, and the prospects for continued success look promising. He and his team were successful in a trial to see whether they could isolate a single antibody from among a thousand million others, and to convert it into a useful test for a weapon of mass destruction within a day. The pipeline allows the scientists to operate within closed environments (in our case the toxin BSL-2 or the hot zone BSL-4) from start to finish without requiring extraneous techniques or instruments to deliver the stop-gap assays. Being self-contained accelerates the entire process and should enable a rapid response to emerging threats of the future.

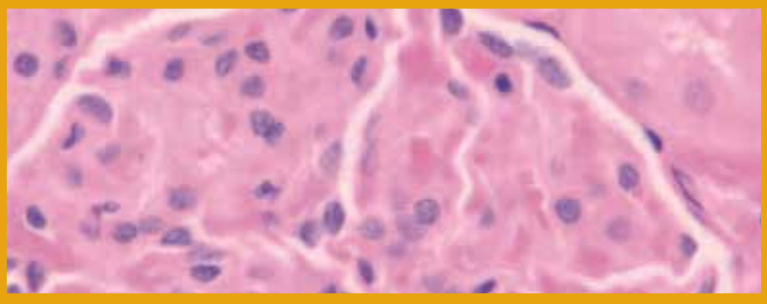
Ruth Ruprecht, M.D., Ph.D., formerly of the Dana-Farber Cancer Institute and Harvard Medical School, is the newest Scientist to join the department. She is a pioneer in developing novel and creative strategies for a vaccine against AIDS, and for preventing mother-to-child transmission of HIV. She also directs the Texas Biomed AIDS Research Program. She and her research team have discovered a new mechanism by which certain antibodies can prevent AIDS virus infection in monkeys.

Patterson continues to work with Carrion and many members of the veterinary staff at the Southwest National Primate Research Center (SNPRC) to utilize the marmoset as an exceptional model for human disease. Working with Emory University, Texas Biomed utilized the marmoset as a model for filovirus vaccine development. The primary advantage of the macaque model is that it is safer to work with than other nonhuman primates in high containment. In addition, primarily working with predoctoral student Jesus Alonso, they have attempted to understand the differences in virulence between two strains of Marburg virus. Using molecular probes they determined that intergenic regions play a role, as does the strain's interaction with cellular proteins.

Assistant Scientist Marie-Claire Gauduin, Ph.D., continues to develop her novel epithelial stem cells AIDS vaccine strategy to elicit a long-term immunity to prevent HIV infection at the site of viral entry. She has also been involved with the establishment of an SIV-resistant macaque model using Zinc Finger Nucleases (ZFN) technology to eradicate HIV infection. She is pursuing her work on understanding the immunopathogenesis of HIV in the newborn/infant macaque model, and has recently developed a suitable neonatal macaque model to study latent mycobacterium tuberculosis infection in pediatric AIDS with veterinary staff at the SNPRC.

Griffiths' laboratory works to understand how highly pathogenic zoonotic agents cause disease, and to develop vaccines and therapies to combat these diseases. In a study published in the *Journal of Virology* with Richard Longnecker at Northwestern University, they reported that herpes B virus — a virus of monkeys that is deadly when it infects humans — uses a different mechanism to infect cells than the closely related herpes simplex virus (cold sores). They are currently investigating whether this has a role in pathogenesis.

The goal of all of this work is to combat and defeat some of the major agents of infectious diseases that threaten the lives of millions, from San Antonio and throughout the United States to most countries worldwide.



"It is essential that scientists understand the pathogenesis of disease in relevant model systems in order to identify effective vaccines and therapeutics against hemorrhagic fever."

Ricardo Carrion Jr., Ph.D.

Associate Scientist, Virology and Immunology

Hemorrhagic fever is an illness caused by several distinct families of viruses; many have no cure. Filoviruses, such as Ebola virus and Marburg virus, are examples of agents that induce hemorrhagic fever and for which mortality can be 90 percent. The increased frequency of outbreaks of hemorrhagic fever caused by Ebola and Marburg in central and western Africa and the potential use of such agents as biological weapons underscore the need to understand pathogenesis of these viruses and to develop effective intervention strategies. These viruses have also been responsible for an 88 percent decline in the world's chimpanzee populations since 2003. Carrion's research program uses Texas Biomed's biosafety level 4 (BSL-4) laboratory to safely study these agents and advance the development of vaccines and therapies for hemorrhagic fever.

In support of filovirus vaccine development, Carrion and his colleagues have developed the common marmoset as a nonhuman primate model for Ebola and Marburg hemorrhagic fever. Marmosets are small, New World monkeys weighing less than 400 grams. A single intramuscular injection of 10 PFU of either virus was sufficient to induce hemorrhagic fever resembling human infection. Animals experienced weight loss, fever, high virus titers in tissue, thrombocytopenia, neutrophelia, high liver transaminases as phosphatases and disseminated intravascular coagulation. The other striking finding in these animals was lymphoid necrosis and lymphocytic depletion observed in spleen. These findings provide support for the use of the common marmoset as a small nonhuman primate model for filovirus induced hemorrhagic fever. This identification is important because these rodent-size nonhuman primates are more predictive of therapeutic efficacy than traditional small animal models.

The second focus of Carrion's research is development of candidate vaccines for hemorrhagic fever. Most recently Carrion and his colleagues have been awarded contracts to test the efficacy of several vaccine platforms against filoviruses. Vaccines being tested by Carrion's team include 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.

In addition to developing vaccines to Ebola and Marburg, Carrion is involved in advanced development of vaccines to South American arenaviruses. The viruses he studies are the causative agents of Bolivian hemorrhagic fever and Argentine hemorrhagic fever. He has recently demonstrated the efficacy of an alphavirus-based vaccine for preventing disease in a small rodent model.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=97**

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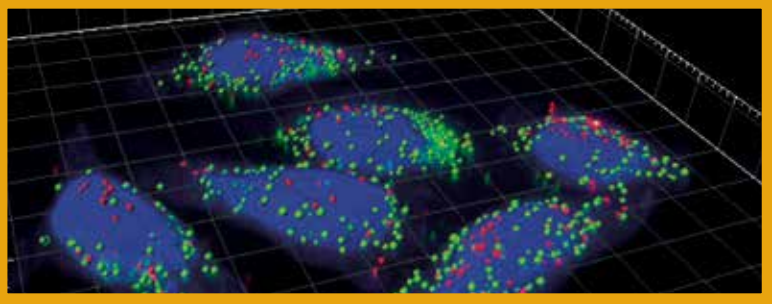
Staff

Left to right: Hilary Staples, Michele Reynolds, Anysha Ticer, Ricardo Carrion Jr., Jerritt Nunneley



"After only two years at Texas Biomedical Research Institute my group has made significant progress toward finding new drugs to treat disease caused by Ebola virus and other deadly viruses. We have two drug candidates that are now validated in rodent animal models. We have also revealed two new aspects of how these viruses infect our cells that will lead to additional treatments not only for Ebola virus but likely for other enveloped viruses."

Robert A. Davey, Ph.D.

Scientist, Virology and Immunology

Scientific research has four avenues of investigation that are being championed by each of Davey's lab personnel. The drug discovery work is mostly being performed by Manu Anantpadma, Ph.D. He has been responsible for sieving through a drug screen performed with scientists at the National Center for Advancing Translational Sciences, which is part of the National Institutes of Health. With their help he tested 350,000 chemicals for ability to block Ebola virus infection. He is now down to 314 chemicals that work very well and Davey's team is collaborating with scientists at the Southwest Research Institute and Purdue University to turn them into drugs. The exciting aspect of the work is that 100 of these chemicals also stop infection by other viruses and so may be broad-spectrum antiviral therapies.

Olena Shtanko, Ph.D., has made an important finding that Ebola virus is a master manipulator of the cell in terms of controlling movement of proteins to the cell surface. She found cell proteins that are normally controlling removal of toxins from the cell are usurped by the virus to drive infection. The mechanism appears to be controlled by virus spike proteins contacting the cell to bind receptors that activate and signaling enzyme called PI3 kinase. Davey expects that this mechanism will be important for other viruses and is teaching us that the interaction of virus and cell is more complicated than previously thought. Interestingly, this same enzyme is often mutated in cancer cells and so virus disease may have features and potential treatments shared with cancers.

Yasuteru Sakarai, Ph.D., has now shown that Ebolavirus requires activation of a special type of calcium channel found inside cell vesicles. This protein behaves like a junction signal control on a railway line. The virus needs to turn the signal to green so it can move onto a special track that allows it to infect the cell. Surprisingly, a Chinese herbal-derived drug is able to stop the virus activating the signal and stops infection in the culture dish. Furthermore, normally Ebola virus will kill mice in five days, but this drug cured the animals. The team is hoping to get new funding to see if this same herbally derived drug could cure infected monkeys.

Technician Ann Reyes is working on a new idea to solve a longstanding problem in the virus community concerning where viruses actually penetrate into the cell. This work is being made possible by a new confocal microscope in our lab, courtesy of the Ewing Halsell Foundation. This microscope will help to make very precise measurements of how and when the virus pushes through the cell membrane to start infection and will be a key tool in learning more about viruses and finding new drug treatments.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=185**

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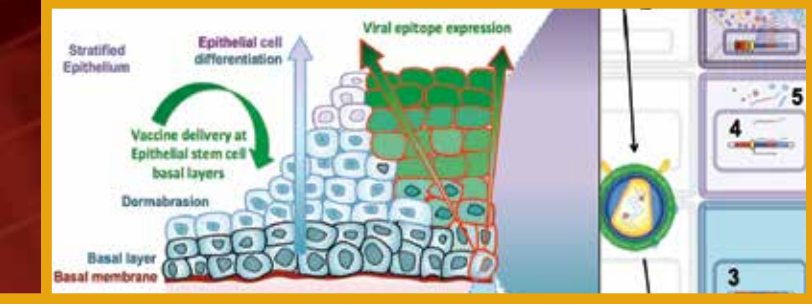
Staff

Left to right: Yasuteru Sakarai, Olena Shtanko, Robert Davey, Manu Anantpadma, Ann Reyes



"Our laboratory is focusing in the SIV/macaque model for AIDS and TB to: 1) understand the early events of HIV transmission; 2) investigate the development of specific immune responses in newborn and infants; 3) develop novel mucosal AIDS vaccine strategies; and 4) study the mechanism of TB/HIV coinfection in pediatric AIDS in order to design better treatments."

Marie-Claire Gauduin, Ph.D.

Associate Scientist, Virology and Immunology

Knowledge of the initial target cells involved in mucosal HIV transmission is still evolving. Gauduin's laboratory is investigating the early events of SIV transmission in macaques using a recombinant SIV tagged with a "green fluorescent protein" as a sensitive tool to monitor infected cells *in vivo*. This construct allows the team to identify: 1) the initial infected cells, their phenotype and function; 2) the mechanisms involved, time course and routes of viral spread from the site of initial infection to lymphoid organs and blood; and 3) the generation of early SIV-specific immune response from the mucosal site of infection. This is critical for the development of effective vaccines.

The development of a safe, effective, easily administered and inexpensive AIDS vaccine is urgently needed to resolve the current HIV-1 acquired immunodeficiency syndrome (AIDS) epidemic. One key obstacle to an effective AIDS vaccine has been the inability to deliver antigen for a sufficient period of time, leading to weak and transient protection. Because HIV transmission occurs predominantly across mucosal surfaces, the ideal vaccine strategy would be to target HIV at mucosal entry sites of transmission to prevent infection. Gauduin proposes to develop a novel genetic vaccine strategy that delivers viral proteins. A promoter will drive antigen expression and stem cells will continuously yield new (daughter) antigen-producing cells without being eliminated by the immune response.

Maternal transmission of HIV-1 accounts for most cases of pediatric HIV-1 infection. Gauduin's group is investigating the early virus-specific T cell responses in neonates orally infected with a pathogenic or nonpathogenic strain of simian immunodeficiency virus (SIV), an HIV laboratory surrogate. She has 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.

The laboratory is now focusing on defining the mechanisms involved in oral SIV transmission to develop effective strategies to successfully block SIV transmission.

Tuberculosis is the leading cause of death among people with HIV, and pregnant women living with active TB and HIV are at far greater risk of maternal mortality than those without HIV infection. Gauduin has successfully established experimental acute (Mtb) aerosol infection in the newborn/infant primate model to produce progressive and/or active but asymptomatic infection that mimics clinical and bacteriological characteristics of Mtb infection as seen in human newborns/infants. Gauduin produced evidence that newborn macaques can be infected with aerosolized Mtb, which make them an ideal animal model to study pediatric TB. This work provides a unique opportunity to understand early immune responses, gain deeper insights into the immunopathogenesis of pediatric TB and TB/HIV co-infection and investigate the efficacy and safety of cocktail treatments and vaccine strategies.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=126**

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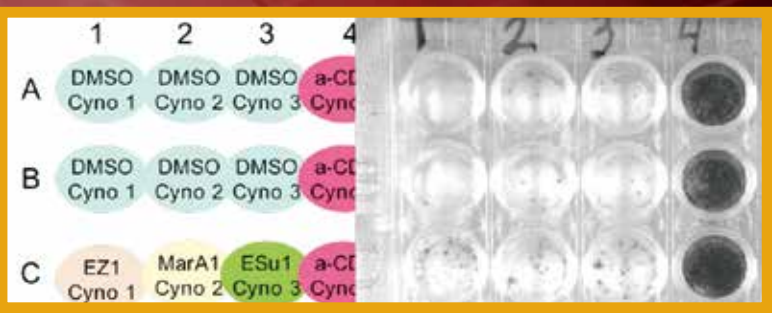
Staff

Left to right: Fuchun Zhou, Mary Salas, Marie-Claire Gauduin, Robert (Bobby) White, Magdalena Cepeda



"My principal research interests include the study of viral infections and the development of vaccines against such infections. Our laboratory specifically works in understanding the innate and adaptive immune responses to retroviral infections in natural and experimental animal models, and in identifying correlates of vaccine-induced protection against infection with filoviruses."

Luis D. Giavedoni, Ph.D.

Scientist, Virology and Immunology

Giavedoni's laboratory studies the role of cytokines and co-stimulatory proteins, molecules that mediate communication between the immune system and the whole organism. His team has been developing reagents for the identification of cytokines in nonhuman primates and also studying the potential use of these molecules to modify the outcome of immune responses.

During 2013 the group continued to carry out studies in AIDS vaccine and treatment development using the rhesus macaque/simian immunodeficiency virus (SIV) model. One project involved the use of biodegradable nanoparticles carrying small nucleic acids designed to bind and inactivate the viral genome within infected cells; proof-of-concept studies in SIV-infected monkeys showed that these particles can transiently reduce virus in circulation. Giavedoni's lab has also been working to identify the bases for resistance of the baboon to infection with SIV. While rhesus macaques become infected with SIV and develop immunodeficiency, baboons are naturally resistant to this infection. In their natural habitat in Africa, baboons overlap with many nonhuman primate species that carry their own SIV; however, no active SIV infection has been identified in baboons in the wild, and they also eventually control experimental SIV infections. Identifying genes responsible for this infection may provide opportunities for new treatments against AIDS. Finally, this group has developed and validated ELISA, ELISPOT, and Luminex cytokine assays to identify and quantify macaque immune responses against the glycoprotein of several filoviruses (Ebola and Marburg virus); the goal is that these assays will allow the researchers to identify the type of immune response to vaccination that can protect against exposure with these deadly viruses.

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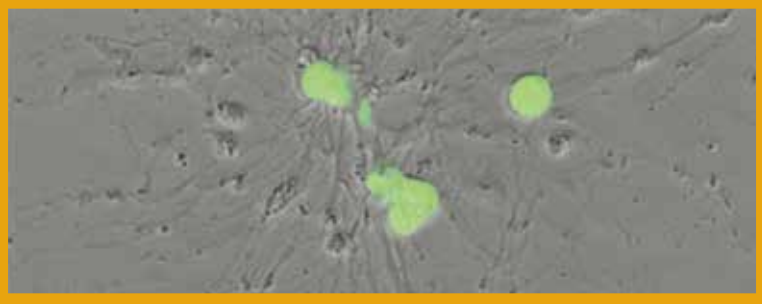
Giavedoni's laboratory also serves as the Immunology Core Laboratory for the Southwest National Primate Research Center. It supports the work of other scientists by: 1) providing assays based in flow cytometry for the characterization and isolation of blood cell subsets and the determination of cell mediated activity (T-cell proliferation, cytotoxic and natural killer cell activity) in nonhuman primate species; 2) providing methodologies for the simultaneous determination of multiple cytokines and chemokines in biological fluids derived from nonhuman primate species; and 3) identifying certain herpes and retroviral infections in macaques from the SNPRC breeding colony.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=31**

Staff

Left to right: Jessica Callery, Luis D. Gaivedoni, Vida L. Hodara, Veronica Obregon-Perko, Laura M. Parodi

Not shown: Lisa M. Smith



"Our long-term goal is to understand how viruses cause diseases in humans. Armed with this knowledge, we will be able to design countermeasures — both antivirals and vaccines — to protect us from infection."

Anthony Griffiths, Ph.D.

Associate Scientist, Virology and Immunology

Griffiths' laboratory studies the most dangerous pathogens, which are those that require BSL-4 containment. In particular, the focus is on Ebola virus and herpes B virus.

Ebola virus causes hemorrhagic fever with a case fatality rate of up to 90 percent and is associated with periodical outbreaks in Africa. However, it is a significant biothreat because of the possibility of spread to new geographic regions and because it is thought to have been weaponized. Consequently, it is a CDC Category A agent that poses a risk to national security. Our work is focused on understanding how this virus causes disease and to support the advanced development of countermeasures that can be used to treat or prevent infection. To this end we are employing a variety of state-of-the-art and classical techniques that range from ultra-deep sequencing to electron microscopy.

Macaque monkeys are indispensable for biomedical research, particularly in studies of HIV/AIDS and biodefense pathogens. Herpes B virus is the macaque equivalent of herpes simplex virus (cold sores) and in macaque colonies, most animals are infected during their first few years of life. In monkeys, herpes B virus causes a minor self-limiting disease. In dramatic contrast, human infection with herpes B virus is typically fatal. A major focus of our herpes B virus research is to understand the molecular mechanisms that cause herpes B virus to be deadly in humans but relatively benign in monkeys. Importantly, these studies are also identifying the mechanisms exploited by herpes simplex virus to cause disease. Using a primary macaque neuronal cell culture system, we are beginning to understand the mechanisms used by these viruses to replicate following extended periods without replication.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=131**

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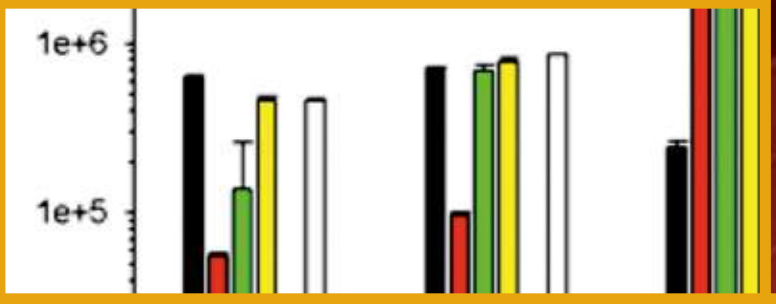
Staff

Left to right: Gabi Worwa, Kendra Alfson, Anthony Griffiths, Mike Beadles, Melanie Amen (seated), Laura Avena



"Work in my laboratory is primarily concerned with developing disruptive technologies for the detection and inhibition of pathogens, toxins and disease states. One aspect of this is engineering a pipeline to rapidly deliver antibodies to any given target of interest that can be immediately assembled into assays without modification or purification, thereby eliminating huge burdens in cost and time."

Andrew Hayhurst, Ph.D.

Associate Scientist, Virology and Immunology

A particularly convenient antibody format to work with is the llama single domain antibody (sdAb) since it is easily produced in *E. coli*, enabling inexpensive laboratory-scale production of large amounts in contrast to tissue culture production of murine/rabbit monoclonal antibodies. Furthermore, sdAb are quite heat stable and often highly refoldable, enabling assays to be made to withstand cold-chain free environments *and* endowing them with the potential to be recycled *ad infinitum*.

Hayhurst's team has generated sdAb specific for Marburg virus and Ebola viruses, which are highly lethal African hemorrhagic fever viruses on the Centers for Disease Control "bioterror" threat Tier 1 list. Remarkably, all of the sdAb hone in on a small, highly conserved region of nucleoprotein that appears to act as a "cryptotope" or hidden epitope that only reveals itself upon disruption of viral particles. Importantly, the nucleoprotein still remains as a polymer to allow a single sdAb to be highly effective in both capturing and tracing the target in a very sensitive Velcro like manner. Working with their collaborators — structural biologists Alex Taylor and P. John Hart of the University of Texas Health Science Center — they are gaining insights into how the sdAb bind the cryptotopes so well using X-ray crystallography.

Another group of Tier 1 biothreats of interest to Hayhurst are the botulinum neurotoxins, which are the most poisonous substances currently known — estimated to be 100 billion times more toxic than cyanide. The toxins are synthesized by certain species of spore-forming anaerobic *Clostridia* bacteria as a variety of immunologically distinct "serotypes," with some of these having several distinguishable subtypes. Hayhurst's team has succeeded in engineering a heptaplex assay for the seven known serotypes and recently showcased the sdAb generation pipeline and screening system in replicating a portion of this work for serotype A within days as opposed to several months.

Hayhurst's laboratory is also developing a new avenue of investigation to develop novel therapeutics for specific types of cancer by exploring new ways of leveraging the potential of tumor-targeting bacteria more effectively.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=74**

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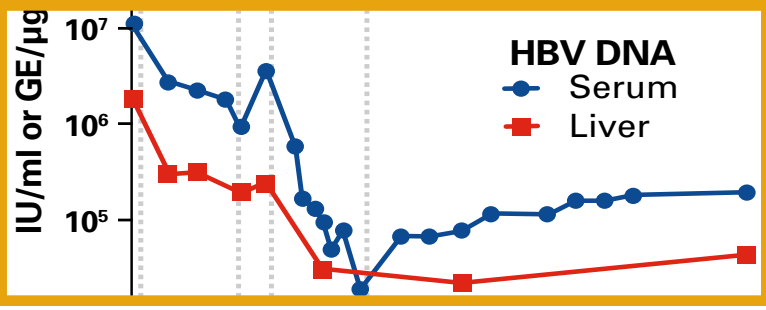
Staff

Left to right: Tamarand Lee Darling, Larissa Helen Mühlenbeck, Andrew Hayhurst, Laura Jo Sherwood, Divya Nandamudi



"The best approach to halting the epidemic of hepatitis C virus-associated liver disease and liver cancer is to cure the viral infection. Today, after decades of effort, the scientific community has produced a cure for HCV. From basic research in the lab, to preclinical trials in chimpanzees and finally to trials in HCV-infected patients, we now have a simple once-a-day pill that will cure greater than 95 percent of patients in 12 weeks."

Robert Lanford, Ph.D.

Scientist, Virology and Immunology

The laboratory of Robert Lanford is involved in research programs addressing hepatitis B virus (HBV), hepatitis C virus (HCV) and GBV-B virus, a surrogate model for HCV. The lab is also developing a novel primate model of liver cancer, a disease caused by hepatitis viruses.

One of the primary focuses of Lanford's research program is to better understand the interactions of hepatitis viruses with the host, and how this influences either viral clearance or chronic infection and progression to advanced liver disease and liver cancer. The focus has been on the innate immune response to the virus and how it regulates the induction of interferons, which are induced in HCV infection and trigger the expression of nearly 1,000 genes in the liver. In a multiinstitute collaboration with Drs. Walker and Lemon, Lanford recently compared the immune response to HCV and hepatitis A virus (HAV), a virus with many similarities to HCV except that it never induces chronic infection. Remarkably, they discovered that during HAV infections almost no induction of interferon response genes occurs in the liver. Thus, the virus that evades the innate immune response is always cleared and the one that induces a robust innate immune response often causes chronic infection. The studies on HAV unveiled a number of surprising findings. These studies highlight the limitations of our understanding of how HCV persist in the liver, and the need for research on persistent viral infections to aid in vaccine development.

Another goal of his program is to help bring new antiviral therapies to the clinic. During the past several years, Lanford's group has tested dozens of new inhibitors of HCV and HBV, many of which have progressed to human clinical trials and some of which are components of the new cocktails with high cure rates for HCV. One of the antivirals examined by Lanford sequesters a liver-specific microRNA, miR-122, that is essential for HCV persistence. The drug SPC3649 (Miravirsen in the clinic) was developed by Santaris Pharma and is the first example of an antisense therapy that is highly efficacious when administered systemically. The success of the drug relies on the Santaris technology called locked nucleic acid (LNA). Lanford is now using the LNA technology and the GBV-B surrogate model of HCV to elucidate the key factors in the innate immune response that are required to orchestrate the adaptive immune response and eliminate the virus. This research will also develop a small primate model for gene knockdown using the marmoset and LNA technology.

This year Lanford published on an exciting new technology that stimulates the innate immune response to combat chronic HBV infection. The technology developed by Gilead Sciences uses a small molecule to stimulate the Toll-Like Receptor 7, which in turn stimulates both the innate and adaptive immune responses. The drug GS-9620 has entered human clinical trials for HBV.

▶ For more information, please visit www.txbiomed.org/departments/virology/virology-staff-bio?u=20

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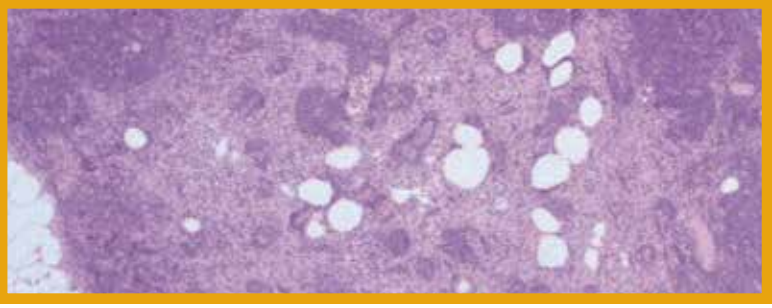
Staff

Left to right: Helen Breton, Bernadette Guerra, Robert Lanford, Deborah Chavez, Lena Notvall-Elkey



Texas Biomed's Department of Virology and Immunology develops vaccines and therapeutics against highly lethal viral pathogens, and determines how they replicate and spread through basic and applied research. To defeat viruses that cause AIDS, hepatitis, herpes, hemorrhagic fevers, and a host of other illnesses, our scientists approach viruses on two different fronts. First, they examine how viruses replicate and propagate in order to identify their vulnerability. Second, they study how the immune system recognizes a virus and how best to stimulate immune response to clear viral infections."

Jean L. Patterson, Ph.D.

Scientist and Chair, Virology and Immunology

Since the anthrax attacks in 2001 the U.S. government has been committed to developing countermeasures to potential biological weapons, now referred to as select agents. Texas Biomed has had a BSL-4 maximum containment laboratory since 2000, in which Patterson's laboratory has worked to develop countermeasures against many select agents. Her group works to develop therapies and vaccines against naturally occurring pathogens that can cause sporadic but lethal outbreaks. Patterson has helped develop three vaccines against Ebola, one with Emory University, one with Crucell Pharmaceuticals and one with Bavarian Nordic, all of which are undergoing further studies. The laboratory has 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. It infects more than 500,000 persons every year with approximately a 10 percent fatality rate and many different forms of lasting effects. The Department of Defense and NIH are committed to an Ebola and Marburg vaccine by 2015; Patterson's group is working with them toward this goal.

Along with Ricardo Carrion Jr., Ph.D., an Associate Scientist in the Department of Virology and Immunology, she has developed the marmoset as a model for many infectious agents. The marmoset is a small nonhuman primate that is not readily available to researchers. Its size and behavior make it a much better model than other larger and more aggressive nonhuman primates. To date Drs. Carrion and Patterson have utilized the marmoset for the model development of Eastern Equine Encephalitis virus, Lassa fever virus, and Ebola and Marburg virus. The pathogenesis of these viral diseases in marmosets closely mimics that of human disease.

The BSL-4 laboratory is utilized by the federal agencies DOD, NIH, FDA and FBI for studies that require specific capabilities. It is also utilized by pharmaceutical companies for testing of new treatments and vaccines against all highly lethal and contagious pathogens.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=33**

Publications

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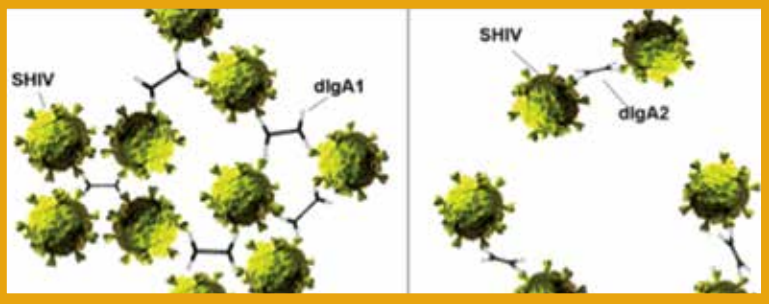
Staff

Left to right: John Koprivsek, Manasi Tamhankar, Michele Reynolds, Daniel Mitchell, Jean Patterson, Jerritt Nunneley

Not shown: Anysha Ticer, Hilary Staples



"More than 90 percent of all HIV infections worldwide occur through mucosal exposure, and more than two-thirds involve the HIV genetic subtype C (HIV-C) that predominates in developing countries, especially in sub-Saharan Africa where the AIDS epidemic is widespread and where the most lives have been lost to this deadly infection."

Ruth M. Ruprecht, M.D., Ph.D.

Scientist, Virology and Immunology

Ruprecht's group has constructed a panel of chimeric simian-human immunodeficiency viruses (SHIVs) that carry HIV subtype C envelopes, giving rise to SHIV-Cs. These viruses allow the evaluation of antibodies targeting the HIV-C envelope in rhesus monkeys, in which SHIV-Cs can replicate and induce AIDS.

In earlier studies, her team has shown that combinations of human monoclonal antibodies (hmAbs) that neutralize HIV in cultured cells can prevent mucosal SHIV acquisition in neonatal macaque models, even when given a post-exposure prophylaxis. These initial passive immunization experiments involved immunoglobulin G (IgG) antibodies administered systemically. Since the most important antibody form in mucosal secretions is immunoglobulin A (IgA), Ruprecht's group tested whether hmAbs given mucosally as IgA forms could prevent mucosal SHIV transmission in macaques. Unexpectedly, recombinant monoclonal versions of the two human dimeric IgA (dIgA) isoforms with the same epitope specificity differed in their ability to protect rhesus macaques against mucosal SHIV-C transmission; dIgA1 was significantly more potent in preventing infection in the monkeys than the dIgA2 version. This difference was linked to a significantly better ability of dIgA1 to bind and cross-link virus particles, thus blocking their passage across mucosal layers. Structural analysis revealed that the antigen-combining sites are father apart in dIgA1 than in dIgA2, allowing the former to capture twice as many virus particles. The team is now focusing on approaches to induce protective mucosal IgA responses by vaccination.

One of the Ruprecht laboratory's long range goals is to prevent maternal HIV transmission with a combination of passive plus active immunizations. Using various recombinant viral proteins as active immunogens, the Ruprecht group has achieved significant protection of SHIV-C-challenged macaques. It is currently analyzing the antibody repertoire of these vaccine-protected animals using a novel biopanning technique. This innovative approach has allowed them to identify an unexpected correlate of antibody-linked protection: neutralizing antibody responses against Tat, one of the small regulatory proteins encoded by all AIDS viruses. Cellular immune responses against this vaccine target have also been linked to complete protection from infection. The team is now pursuing novel approaches based upon bimodal immunization that seeks to induce both strong cellular and humoral immunity.

▶ For more information, please visit **www. txbiomed.org/departments/virology/virology-staff-bio?u=194**

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Staff

From left to right: Ashley Ladd, Juan Esquivel, Joshua Owuor, Ruth Ruprecht, Muhammad Mukhtar, Samir Lakhashe, Anton Sholukh, Mingkui Zhou, Hemant Vyas

Southwest National Primate Research Center

On June 1, 1999, the Southwest National Primate Research Center (SNPRC) became the first new NCRR-funded National Primate Research Center (NPRC) established since the early 1960s. The SNPRC brought a number of unique strengths to the NPRC program, stemming from a long, productive history of nonhuman primate research at its host institution, the Texas Biomedical Research Institute. These unique strengths include the world's largest captive baboon population, the world's largest and best-characterized pedigreed primate population, the world's largest group of geneticists committed to research with and management of captive nonhuman primates, the largest chimpanzee census of any NPRC, and a veterinary technical staff experienced in the management and use of diverse species of nonhuman primates ranging from chimpanzees to marmosets.

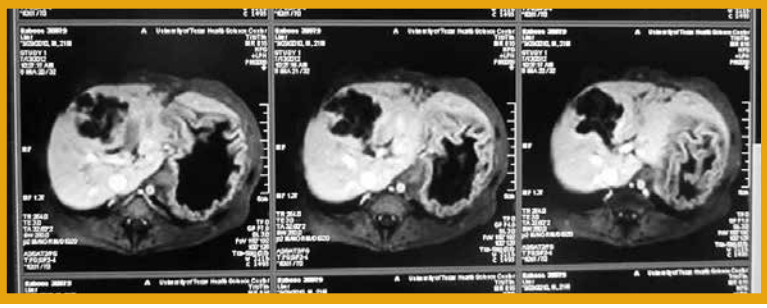
Since its designation, the SNPRC has enhanced those strengths and has developed new ones, including a marmoset breeding colony (one of only three at NPRCs), animal biosafety level (ABSL) 3 and 4 facilities for nonhuman primate research (the only ABSL-4 facility at an NPRC) and a baboon gene linkage map (the first for any nonhuman primate species). The SNPRC is capitalizing on these strengths and is developing new animal and technical resources.

The SNPRC provides investigators opportunities to select from a wide variety of species to meet their research needs and its facilities and range of expertise are appropriate for managing other species that are purchased for investigators when needed. In addition, the SNPRC makes available to genetic researchers the largest pedigreed nonhuman primate population in the world. That pedigree spans seven generations of baboons, the first nonhuman primate species with a detailed gene map, enabling whole genome scans aimed at identifying genes that impact risk factors for diseases.

Overall, the SNPRC has greatly strengthened the biomedical research capacity of the NPRC program. It has brought ABSL-4 research capability to the program and increased ABSL-3 capacity. It has provided unique primate genetic resources, technologies and services to other NPRCs. It has strengthened the emphasis on nonhuman primates as models for a diversity of human diseases by bringing to the program a variety of multidisciplinary technologies in research on common chronic diseases, neonatal diseases, vaccine and drug development, gene therapy and stem cell biology. It also brought to the NPRC program baboon resources and sophisticated technologies for their experimental use. The SNPRC also provides cost-effective primate resources to the only region of the country that did not previously have the benefits of ready access to a National Primate Research Center.

SNPRC leadership: top left to right: John Bernal, Lloyd Phinney, Bill Cummins, John VandeBerg. Bottom left to right: Sarah Williams-Blangero, Lora Boyd

The SNPRC research programs are each assigned to one of three research facilitation groups that bring together all scientists who have shared scientific interests: Infectious Diseases and Biodefense, Metabolic Diseases and Genomics, and Physiology, Behavior, and Basic Medicine. Some investigators belong to more than one group. This structure fosters a high degree of interaction among the various scientific disciplines represented within the SNPRC.



"As a laboratory animal veterinarian I have had the privilege of working with a variety of animals in a research setting and will always remain their staunchest supporter for humane care and use."

Kathleen M. Brasky, V.M.D.
Veterinarian, SNPRC

Brasky's responsibilities include the Southwest National Primate Center's chimpanzee colony, the marmoset and tamarin colonies, and the animal biosafety level 4 laboratory (ABSL4).

The genetic, physiological, biochemical and immunological similarities of chimpanzees to humans make them unique models to study infectious diseases such as the hepatitis viruses and HIV, to test the safety and efficacy of various human monoclonal antibodies and unique therapeutic modalities, and in the production of embryonic stem cells. To maximize the use of this model, the goal of Brasky and her colleagues is to maintain a healthy population of chimpanzees with well defined research and health histories, as well as facilities and the expertise to support their use in biomedical research.

Marmosets are small nonhuman primates commonly used in a wide variety of biomedical disciplines, such as neuroscience, reproductive biology, infectious disease, and behavioral science. The marmoset breeding colony was established in 2004 and has provided animals for a variety of studies ranging from biodefense to diet induced obesity. Brasky's team promotes the use of this small nonhuman primate species in various biocontainment and aging studies, to produce a healthy population of marmosets available for use in biomedical research, and to provide expertise using this model to other investigators. The group also maintains a small colony of tamarins for use in GBV-B research. The use of marmosets continues to expand and new areas of research include developing models of inflammatory diseases and expanding our knowledge of nutrition and gastrointestinal disease.

Brasky is currently working with Robert Lanford, Ph.D., in trying to develop a baboon model of liver cancer and working with Ruth Ruprecht, M.D., Ph.D., on SIV macaque protocols.

Publications

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Staff

Left to right: Laura Condel, Danny Alonzo, Donna Layne-Colon, Melissa de la Garza, Cassandra Bauer, Kathy Brasky, Robert Geiger, Teresa Valverde, David Pineda, Juan Zapata, Joe Vallejo

"The Veterinary Resources staff ensures that each animal's living environment is optimal and that the research is conducted to the highest of animal welfare standards. Highly skilled teams of veterinary research technicians that specialize in primate care provide the ideal research setting. The center's comprehensive training program is designed to allow animal care and technical staff to advance in their fields of expertise and in laboratory animal care and research. The staff is committed to providing animals with the most knowledgeable, dedicated and compassionate animal care possible in biomedical research."

John C. Bernal, D.V.M.

Associate Director for Veterinary Resources and Research Support, Attending Veterinarian

Lloyd Phinney, D.V.M.

Assistant Director for Veterinary Resources

Southwest National Primate Research Center veterinarians and their technicians support all aspects of clinical medicine, pathology, disease model development, surgical model development, infectious disease and biocontainment research methods, reproductive research, and laboratory animal medicine and breeding. Collaborative efforts with Texas Biomed's principal investigators and scientists in the many specialized areas of veterinary medicine provide the expertise needed to optimize the research objective throughout entire research projects from their inception. The veterinary resources team of veterinarians, technicians and support staff aid in study design and in-life study execution as well as providing the information needed to realize the scientific aim.

Veterinary Resources cares for the world's largest captive baboon population, the world's largest and best-characterized pedigreed nonhuman primate populations, and the largest chimpanzee census of any National Primate Research Center. Other valuable nonhuman primate colonies that are managed and cared for by Veterinary Resources include a marmoset breeding colony and an Indian-origin SPF rhesus macaque breeding colony. The unit also cares for a large breeding colony of laboratory opossums and a rodent colony, which are used in research that is preliminary to the use of nonhuman primates. All of these animal colonies are housed in all or part of 72 buildings (236,793 square feet and two six-acre corrals). Support space for the animal care program (78,869 square feet) is located on the periphery of the campus. The animal facilities include both conventional (indoor, indoor/outdoor and outdoor) and ABSL-3 and ABSL-4 containment buildings. State-of-the-art equipment is provided for the staff to conduct and support research efforts of intramural and extramural investigators and collaborators. Multiple surgical suites, animal clinics, and clinical and diagnostic pathology units are available.

Many domestic and foreign veterinarians and pathologists, both pre- and postdoctoral, are trained by the Veterinary Resources professional staff. Seven veterinarians and two veterinary pathologists are on staff. A six-person behavioral team within Veterinary Resources assists the veterinary staff with animal enrichment and training, behavioral modification and abnormal behavior prevention, in addition to providing research support to investigators.

Staff

Left to right: Lauren Suarez, Terry Naegelin, Jennifer Church, Russell Starr, John Bernal, Brooke Bollwahn, Lloyd Phinney, Don Taylor, C.J. Peters, Jahnni Robinson, Julyne Centeno, Michael Washington

"The ultimate goal of biomedical research is to improve the quality of life for all. While fundamental to achieving this goal, the use of animals in research is a privilege that carries with it inherent responsibilities. As a lab animal veterinarian, I play a crucial role in helping investigators to achieve study directives, yet my ultimate responsibility is to the animals under my charge. I strive to provide them the highest possible quality of care throughout the course of study, and indeed, throughout their entire lives."

Melissa A. de la Garza, M.S., D.V.M.

Associate Veterinarian, SNPRC

As the Scientific Manager for the ABSL-3 Laboratory, de la Garza is primarily responsible for the daily operations of the facility. This includes providing leadership for the veterinary technical staff supporting the facility, as well as serving as lead veterinarian for research protocols conducted there.

Realizing that establishment of animal models is integral to the success of any infectious disease program, the SNPRC has assembled a staff of veterinarians, veterinary technicians and pathologists skilled in the care and use of laboratory animals to support our laboratory. Although the facility is equipped to manage all species of laboratory animals less than 10 kg, it specializes in the use of nonhuman primates.

By selecting a dedicated core staff of veterinary technicians with expertise in handling small lab animals, most especially NHPs, in high biocontainment environments, de la Garza can assure investigators that their studies will receive uncompromising attention to detail and their animals will be provided the highest level of care. She and her team thoroughly review study protocols, monitor animals closely and communicate openly with investigators throughout the course of study to facilitate reaching study goals. In order to produce high-quality test subjects, it is imperative that animals be housed in highly enriched environments, with measures taken to reduce boredom and anxiety. With this goal in mind, the staff is encouraged to develop relationships with each animal, learning their likes and dislikes and individual characteristics. The quality of care the animals receive directly reflects the quality of science produced.

In the nearly eight years that the ABSL-3 has been operational, scientists have conducted a number of vaccine development and animal model studies using both select and nonselect agents. Some of these include the use of *Bacillus anthracis* (Ames, Sterne), *Francisella tularensis*, Japanese Encephalitis, West Nile Virus, Dengue Virus, *Mycobacterium tuberculosis (Mtb), Burkholderia mallei* and *Burkholderia pseudomallei*. Animal models used thus far include rhesus macaques, cynomologus macaques, rabbits and mice.

Publications

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De la Garza shares other clinical and research responsibilities throughout the Institute. She provides clinical support for the chimpanzee colony. Chimpanzees 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. The animals benefit from an in-house, highly skilled veterinary support staff as well as the expertise of colleagues from the world of human medicine. She also supports the various animal colonies as required and the ABSL-4 facility.

The ABSL-4 resource is a maximum-containment laboratory that provides the highest level of laboratory containment and the infrastructure to permit a safe working environment on potentially lethal agents, especially those categorized as select agents, in a variety of animals. This is the only such facility located at a National Primate Research Center and it provides a unique capability for *in vivo* research with the most dangerous pathogens in several species of nonhuman primates. De la Garza and her colleagues have developed the expertise to work with a variety of hemorrhagic fever viruses, multidrug resistant bacteria, and various emerging pathogens in rodent, rabbit and nonhuman primate models.

Staff

Left to right: David VanDenberg, Alberto Torres, Kathleen Brasky, George Villanueva, Melissa de la Garza, Laura Rumpf, Mathew Stautzenberger, Tony Bowers

"The pathology staff supports the clinical veterinary staff in maintaining the health of the animal colony, and assists investigators in evaluating tissue changes and interpreting clinical laboratory results from experimental animals. The pathology service improves the characterization of nonhuman primates through collaboration, publication, education and tissue sharing. In addition, it is active in training student interns and foreign veterinarians, and in publishing manuscripts on case reports and epidemiology."

Edward J. Dick Jr., D.V.M.
Veterinary Pathologist, SNPRC

Michael A. Owston, D.V.M.
Veterinary Pathologist, SNPRC

Pathology is a specialty of veterinary medicine that focuses on the examination of tissues to diagnose disease. Pathology is also an academic and scientific discipline that is concerned with etiology and pathogenesis of disease. In the detection and diagnosis of naturally occurring disease, the pathologist acts as a consultant to the clinical veterinarian to establish diagnoses, predict outcomes and evaluate treatment procedures. In research projects, the veterinary pathologist assists the investigator in the design and interpretation of experiments by avoiding common diseases that would confound experiments, by detecting natural animal diseases that may complicate the experiment and by measuring anatomic, chemical, hematologic, serologic, or microbiologic endpoints of interest to the investigator. The role of the veterinary pathologist in animal care and research is parallel to that of the medical pathologist in the practice of medicine and clinical investigation involving humans. The broad objectives of the pathology service are to support the health maintenance and veterinary care of the Southwest National Primate Research Center's nonhuman primate resources, educate interested individuals and assist intramural and extramural investigators in designing and conducting research with these animals.

Specific services include:

- Providing comprehensive anatomic pathology services, including gross examination at necropsy, supplemented by histology, cytopathology, immunopathology, cryopathology, special stains and other specialized techniques as required.
- Providing comprehensive clinical pathology services, including analysis of blood, urine, feces, cerebrospinal fluid, and other bodily fluids by chemical, hematologic, and microbiologic methods.
- Assisting clinical veterinarians and investigators in interpreting pathologic data from nonhuman primates and recording findings for future reference.
- Organizing results from anatomic and clinical pathology assessments to detect disease trends in the Center's nonhuman primates, and to improve the characterization of nonhuman primates for research.
- Working closely with Biomaterials Services to ensure collection and processing of tissues as requested by investigators.
- Educating interested individuals in pathology and laboratory animal medicine.
- Pursuing collaborative research efforts and publishing results in the scientific literature.

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Staff

Left to right: Tony Perez, Kelly Clark, Cathy Snider, Edward Dick, Rosie Cordova, Jerra Pecotte, Renee Escalona, Sam Galindo, Maureen Robbins

Not shown: Michael Owston

"The baboon and macaque section of the Veterinary Resource Division is the largest in terms of animal holdings and diversity of research. We draw upon the expertise of three experienced veterinarians and a large technical staff that have years of experience developing research programs and maintaining well-defined breeding colonies to sustain current experimental demands. We work closely with the scientists to further develop genetically defined animals to meet their research goals."

Patrice Frost, D.V.M.
Cassondra Bauer, D.V.M.
Robert Baker, D.V.M.

The Veterinary Resource Division is closely involved with investigators in protocol development from inception to performance. Among its many projects, the group has investigated the female throughout her cycle. Production colonies have been developed to support early-stage investigations such as IVF, ICSI, SCNT, ET, chimeras and stem cells along with investigations of the fetus throughout the entire gestational period under variable conditions. They have supported multiple programs investigating the neonate that have led to the development of infectious disease protocols in the neonate.

The metabolic group has an extensive program that includes the development of an obesity model in the baboon, metabolic profiling and experimental production of a diabetic model using STZ. They are also developing therapeutic treatment modalities, a surgical model of diabetes and longitudinal investigation of genetic, dietary influences on the cardiovascular system as well as the influence of drugs within the brain on diet. The division has developed surgical models for chronic catheterization, unique surgical devices, valvular transplantation, tissue antigenicity and the exploration of prothesthetic devices. Multiple surgical suites offer the ability to monitor, diagnose and meet the unique needs of these surgical patients with critical postoperative care. Diagnostic equipment includes standard clinical equipment such as endoscope, bronchoscope, digital x-ray, DEXA and ultrasound. The fluoroscope has been essential to the development of protocols that involve interventional procedures such as catheter placement, targeted dosing and gene therapy protocols. The Veterinary Resource Division's ability to perform pharmacokinetic and vaccine development studies is longstanding.

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Staff

Left to right: Sharon Price, Gabriel Hernandez, Travis Church, Patrice Frost, Joe Jimenez, Cassondra Bauer, Nathaniel Wells Jr., Bob Baker, Brian Rodriguez, Verla Atkins, Lateya Smith, John Diaz, Jesus Godinez

"The main goals of the Behavioral Services Program are to provide nonhuman primates an environment that encourages the expression of species-typical behaviors and to develop and utilize state-of-the -art behavioral management procedures that increase the well-being of the animals under our care."

Corrine Lutz, Ph.D.

Leader, Behavorial Services, SNPRC

The Behavioral Services program is built upon accumulated knowledge of the natural history and behavior of each species housed at SNPRC. This knowledge is integral to the development of appropriate behavioral management and enrichment plans that are used to promote animal welfare.

Providing social contact is the best way to encourage natural behaviors of nonhuman primates. A social partner is perhaps the most important and basic environmental variable because it provides constantly changing stimuli and challenges the animal's social and cognitive functioning. Almost all of the primates at SNPRC are housed in pairs or social groups, and Behavioral Services staff members work to ensure compatibility of the group members.

Environmental enrichment also includes structural, manipulable, nutritional, occupational and sensory enrichment. All enclosures are equipped with some form of structural enrichment such as climbing structures, perches or swings, and the animals are also given a wide variety of toys such as hard plastic balls, rubber toys, nylon bones and metal rattles. In addition to the standard nutritional diet, the monkeys and chimpanzees are provided with nutritional enrichment in the form of a variety of fruits and vegetables and additional treats such as yogurt, popcorn or raisins. Some foods are placed in foraging devices or puzzles to create added challenges. Music, mirrors, nature videos and children's television programming are also provided as additional sensory enrichment.

The Behavioral team provides a range of services to support both colony management and research. One responsibility is to train animals to cooperate for routine husbandry, research and clinical procedures.

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This training provides positive human interaction, reduces stress and refines research methods. The Behavioral Services staff members also conduct routine observations on many of the animals to assess their well-being. In situations where an animal may have special needs, a behavioral intervention plan is then instituted. To further educate the staff, Behavioral Services teaches seven classes that cover animal training, environmental enrichment and the ecology, social structure and behavior of nonhuman primates.

Behavioral Services personnel consult with investigators whose projects may be affected by the behavioral abilities, needs and limitations of study animals. In addition, they often make recommendations regarding which animals to use for a given project and develop procedures for collecting behavioral data. Because behavioral problems can negatively impact both research and animal welfare, current research interests for Lutz include identifying risk factors for both abnormal behavior and alopecia, and assessing the association of these conditions with stress and anxiety.

▶ For more information, please visit **www.txbiomed.org/primate-research-center/primate-research-center-staff-bio?u=138**

Staff

Left to right: Heath Nevill, Maribel Vazquez, Brittany Peterson, Corrine Lutz, Elyse Rankey, Colleen Bowman, Blake Harrington
Not shown: Sabrina Bourgeois

"At the forefront of translational medicine, nonhuman primates are often the last critical piece in a research puzzle before a new life-saving process can be applied to humans."

Karen S. Rice, Ph.D.

Leader, Research Coordination, SNPRC

Rice leads the Research Coordination Group of the Southwest National Primate Research Center (SNPRC), which receives processes and coordinates research requests by principal investigators who seek to use the SNPRC's nonhuman primate (NHP) resources. The scientists who access the SNPRC to carry out their work are appointed as affiliates or adjunct scientists. The SNPRC receives more than 100 requests each year.

In 2013, the SNPRC sponsored more than 90 Texas Biomed, affiliate and adjunct scientists with government and private support from around the country in their NHP research endeavors. The Research Coordination Group assists investigators with budgets, protocol development, timelines, schedules and project monitoring. Investigative sponsored work has ranged from repurposing existing drugs to treat deadly pathogens to programming fetal development. Other studies address the role of stem cells in healing damaged arteries, reproductive contraception, genes that influence LDL-cholesterol and the development of a new drug for treating hepatitis B.

The SNPRC has more than 2,400 NHPs: baboons, chimpanzees, macaques and marmosets. This wide variety of primate species gives the SNPRC a special strength in meeting diverse research needs. Research Coordination supports national and international scientists in gaining access to these animals. Texas Biomed research leaders specializing in particular biomedical areas — metabolic disease and genomics, infectious disease and biodefense, and physiology, behavior and basic medicine — apply their scientific expertise to help guide external investigators seeking information on how best to use NHPs to model their study. The result has been a steady increase in the number of investigators who have come for the first time or returned to carry out their studies at SNPRC.

▶ For more information, please visit **www.txbiomed.org/primate-research-center/primate-research-center-staff-bio?u=77**

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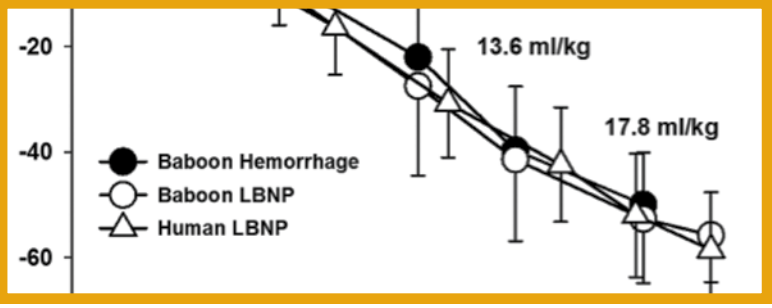
Staff

Left to right: Jennifer Marty, Craig Schmidt, Karen Rice, MJ Bell, Cheri Spencer, John Tobler, Tina Morales



"My research focuses on the interaction between diet composition and genetic factors in cardiovascular regulation. Currently active research projects have been designed to determine how dietary salt, fat and carbohydrate content and genetic influences contribute to the risk for changes in cardiovascular regulation that contribute to complex metabolic diseases."

Robert E. Shade, Ph.D.

Associate Scientific Officer

The research team received a renewal of a major three-year grant from the G. Harold & Leila Y. Mathers Charitable Foundation in 2011. This is a multi-institutional project that includes investigators at the University of Texas Health Science Center San Antonio, Duke University, and the University of Melbourne in Australia. The major objective of this research program is to define the neural mechanisms that contribute to regulation of ingestive behavior such as salt, water or food intake. The recent observation by this group that salt depletion promotes activation of gene networks in the hypothalamus of the brain in rats and mice that have previously been associated with addictive behavior has opened a new direction for this research in baboons. Studies that are currently in progress will explore whether salt and food appetites in baboons can be attributed to activation of these gene networks.

This research program also completed collaborative study with the Institute of Surgical Research (ISR) and Brooke Army Medical Center during the last year. The ISR group uses a lower body negative pressure procedure in human subject studies as a surrogate for the cardiovascular effects that occur with blood loss that is sufficient to cause decreases in blood pressure. This research has demonstrated that 20-30 percent of their test subjects have a low tolerance for LBNP. This is similar to the 20-30 percent of trauma induced blood loss cases where it is difficult to maintain adequate blood pressure with resuscitation treatment. However, the cardiovascular effects of LBNP have never been directly compared to cardiovascular effects of blood removal. The collaborative study accomplished this comparison using anesthetized baboons for the study subjects. This study established that the cardiovascular reflex responses to LBNP and hemorrhage were identical indicating that LBNP is a valid experimental model of the central hypovolemia that occurs with hemorrhage. The ultimate goal of this research at ISR is to develop new technologies that will identify those individuals who have low cardiovascular reserves and need special attention in trauma situations.

We also provide laboratory resources for a staff scientist in the Southwest National Primate Research Center, James Mubiru, Ph.D. Mubiru is funded by an NIH Mentored Research Development Award. The objective of his research is the development of nonhuman primate models of prostate disease. In this research he has shown that male baboons and macaques have serum prostate specific antigen (PSA) levels that increase with age similar to what occurs with aging in men. Mubiru has recently shown that PSA levels decrease in cynomolgous macaques as body mass index (BMI) increases with a high fat/ high carbohydrate diet. Since PSA levels are lower in men with a high BMI these results suggest that cynomolgous macaques are a valid model for investigating the relationship between PSA and BMI.

▶ For more information, please visit **www.txbiomed.org/primate-research-center/primate-research-center-staff-bio?u=18**

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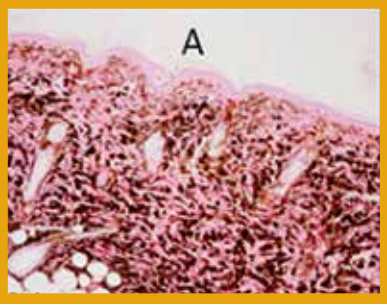
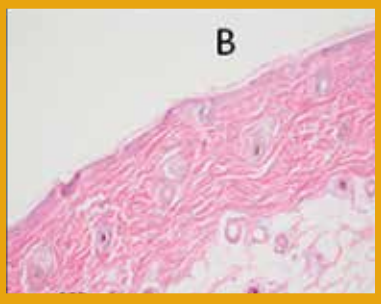
Staff

Left to right: Magdelena Garcia-Forey, Robert Shade, James Mubiru





"My primary research goals are to identify genes and environmental factors that affect physiological processes in healthy and disease states, and to understand the mechanisms by which they exert their effects."

John L. VandeBerg, Ph.D.

Chief Scientific Officer, Texas Biomedical Research Institute
Director, SNPRC
Scientist, Genetics

Nature versus nurture? This has been a timeless question in regard to human behavior as well as to healthy and disease states. Are we primarily a product of the genes we inherited from our parents (nature) or of the environment in which we grew up and currently live (nurture)? The answer is that genes and environment both have profound effects on the behavioral and physiological characteristics of individuals. The premise of VandeBerg's research is that by identifying specific genes and specific environmental factors that influence physiological characteristics, and understanding the mechanisms by which they exert their individual and collective effects, new strategies for preventing and treating diseases can be developed.

In order to pursue their research goal, the group uses Texas Biomed's unique colonies of pedigreed baboons and laboratory opossums, to which they feed several different challenge diets in order to detect genetic and environmental influences on risk of cardiovascular disease. In both species, the researchers have identified genes that affect levels of good cholesterol (LDL) or bad cholesterol (HDL) in the blood when the animals are fed a high-fat diet. Other recent notable findings are that 1) in baboons, the high-cholesterol diet causes senescence of the cells that line the arteries, leading to greater risk of atherosclerosis, but that different individuals are differentially susceptible to this detrimental effect of dietary cholesterol, 2) a variant of a gene known as *ABCB4* causes opossums to develop non-alcoholic fatty liver disease when fed a high-fat diet, 3) sunscreen with SPF15 is highly protective of malignant melanoma in opossums exposed to ultraviolet B radiation, 4) baboon embryonic stem cells can completely restore structure and function to a blood vessel that has been stripped of its inner surface (endothelium).

The use of these pedigreed families of baboons and opossums under carefully controlled environmental conditions enables discoveries that could not be made easily, if at all, in research with human subjects. As the team dissects the genetic and environmental factors that contribute to physiological processes in healthy and disease states, they will be able to translate the knowledge gained to developing new preventions and treatments for human diseases. Toward that goal, they are developing stem cell therapies for repairing damaged arteries in baboons as a model for human subjects.

▶ For more information, please visit **www.txbiomed.org/primate-research-center/primate-research-center-staff-bio?u=71**

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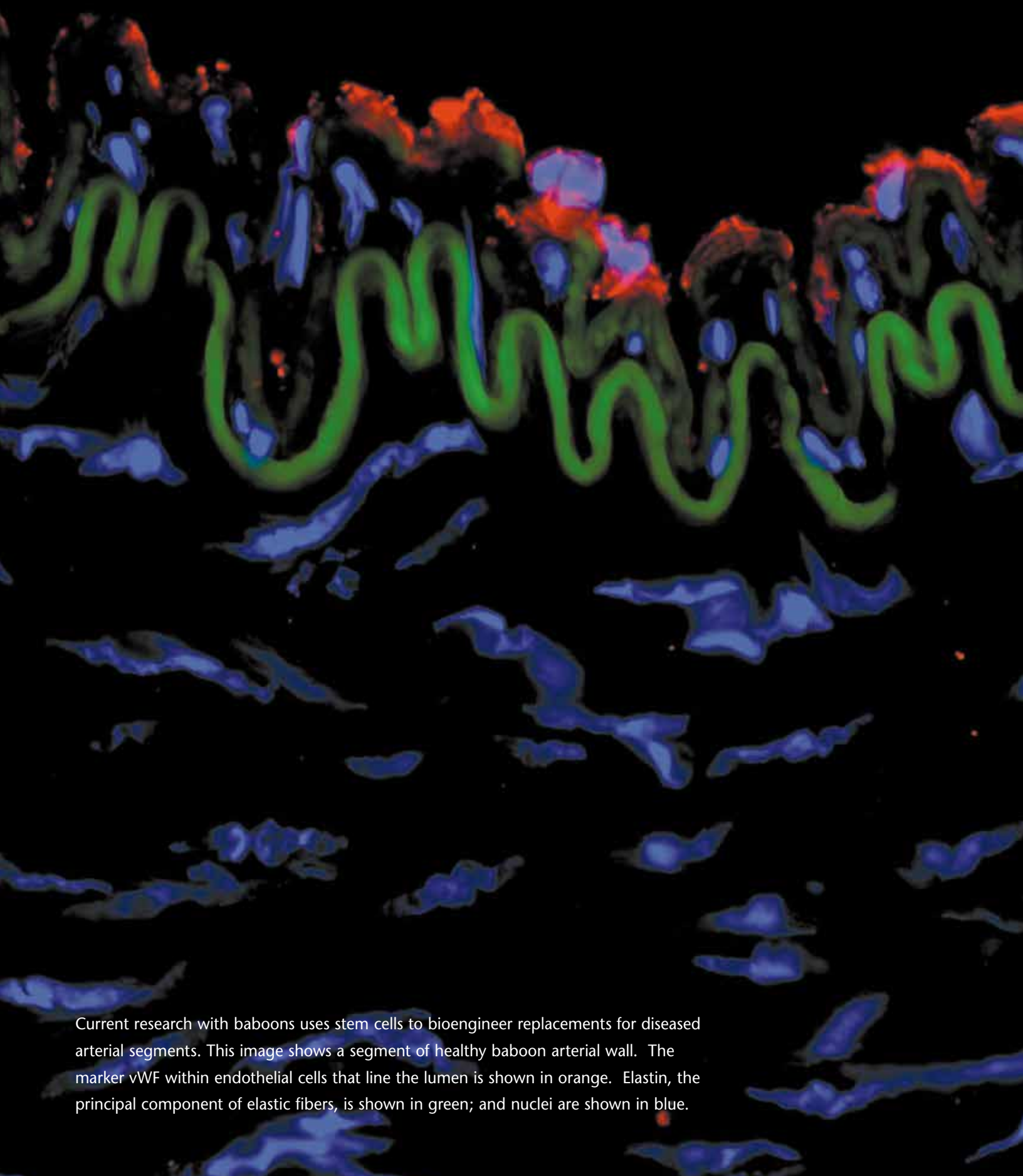
Staff

Top left to right: Qiang Shi, Hareesh Nair, Don Taylor, John VandeBerg, Rick Carranza, Cheri Spencer, Sam Galindo. Bottom left to right: Xiaoming Zhang, Susan Mahaney, Jane VandeBerg, Mari Hui, Heather Guenther, Ernesto Morin



Current research with baboons uses stem cells to bioengineer replacements for diseased arterial segments. This image shows a segment of healthy baboon arterial wall. The marker vWF within endothelial cells that line the lumen is shown in orange. Elastin, the principal component of elastic fibers, is shown in green; and nuclei are shown in blue.

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