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Scientific Report

2011–2012

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Cover: This image shows an endothelium monolayer formed from embryonic stem cells on the inside of a baboon blood vessel, with endothelial cells stained pink and red, and smooth muscle cells stained green. The blue color represents nuclei of all cells.

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Published March, 2012

TEXAS BIOMEDICAL
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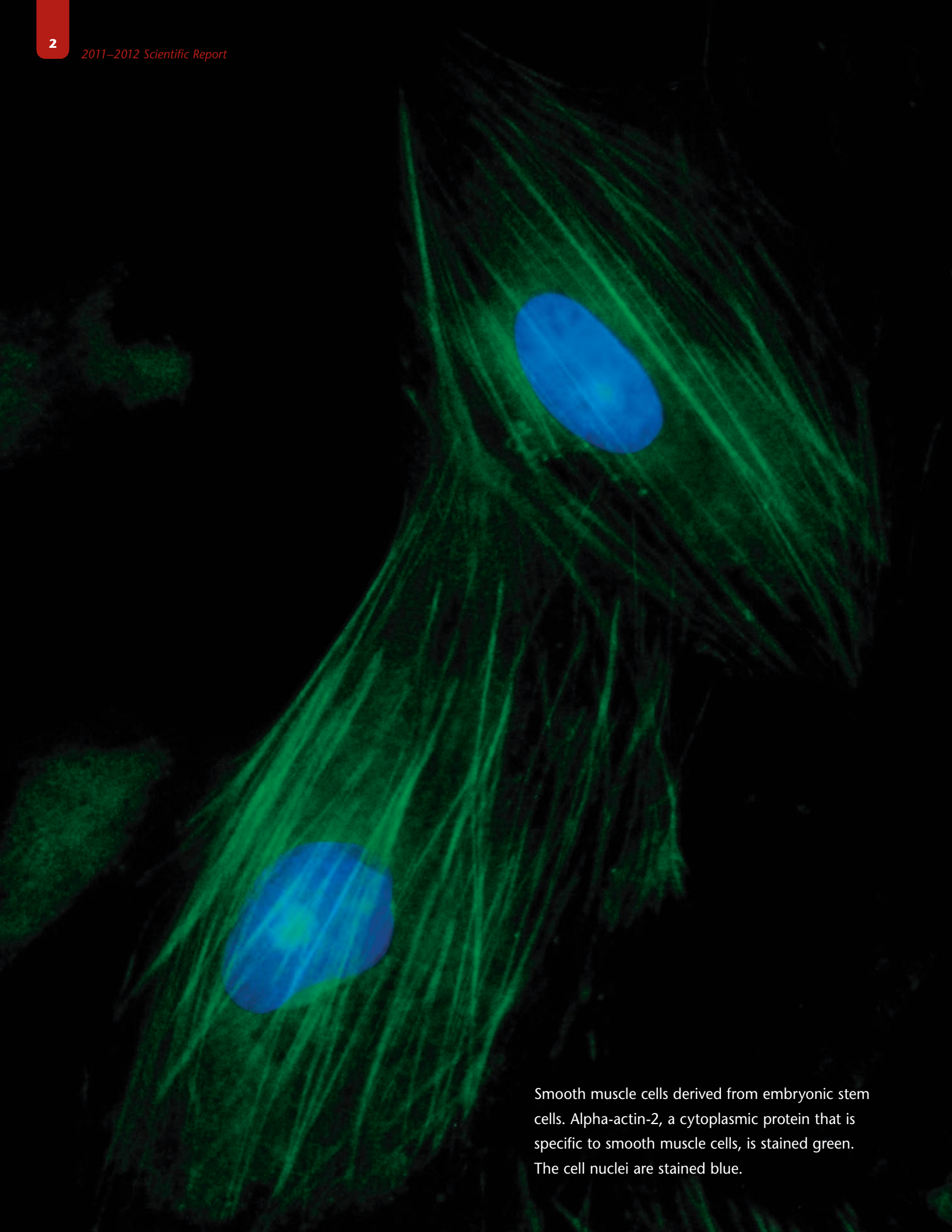


Smooth muscle cells derived from embryonic stem cells. Alpha-actin-2, a cytoplasmic protein that is specific to smooth muscle cells, is stained green. The cell nuclei are stained blue.

Letter from the President

Dear Friends and Colleagues,

I am very pleased to share with you the 2011-12 biennial Scientific Report for the Texas Biomedical Research Institute, formerly known as the Southwest Foundation for Biomedical Research. We changed our name effective February 1, 2011 to better identify what we do and to avoid confusion with our sister institution, the Southwest Research Institute.

We hope this summary of research activities will be helpful to other academic organizations, scientists and scientists-in-training, pharmaceutical and biotechnology companies who may wish to interact with our researchers or utilize our non-human primate colonies, community leaders, federal agency personnel, and public officials. This publication is not intended to replace our Annual Report, which is focused on a broader audience, but to supplement our communications with individuals, groups and organizations who should know about our research efforts and unique combination of scientific resources.

Texas Biomed has been an extraordinary source of intellectual capital for seven decades. The basic and translational research efforts here have deepened our understanding of the genetics of complex disorders, virally-induced diseases, normal physiology and many of the aberrations that lead to disease. All of this work is facilitated by large colonies of non-human primates, an extraordinary computer "ranch" of 8,000 processors that analyze genetic data, the most secure of bio-containment research environments, and human population studies that every day lead to remarkable insights into the pathogenesis of a variety of life-altering and life-threatening human illnesses.

All of these activities are undertaken in the organizational setting of an independent, not-for-profit research institution. This permits us to take prompt advantage of new scientific opportunities, infusions of government and philanthropic support, and the wonderfully collaborative environment of San Antonio.

We take our role as a pioneer in biomedical research in this region very seriously, and I hope this Report reflects that. When Tom Slick courageously founded this institution in December, 1941, there was no medical school in San Antonio, no university hospital, no University of Texas at San Antonio. There was just one important asset, the vision of a man who believed profoundly that basic research could change the world and advance the interests of humankind.

Each day, we try to emulate and reinforce that vision … that extraordinary spirit. We reach out not just to this city, this region, or even to the United States, but to the world-at-large. Disease outbreaks in the most remote regions of the globe can have devastating impacts right here at home. Conversely, new discoveries here can transform the lives of people far from our borders.

"Texas Biomed has been an extraordinary source of intellectual capital for seven decades. The basic and translational research efforts here have deepened our understanding of the genetics of complex disorders, virally-induced diseases, normal physiology and many of the aberrations that lead to disease."

I invite you to read about our work and to share in our mission. Improving the health of our global community is not just what we stand for; it is what we do every day.

Kenneth P. Trevett, JD
San Antonio, 2012

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.

Recent research highlights include:

- Demonstration with baboons that even a moderate reduction in maternal nutrition during pregnancy has a detrimental impact on brain development of the fetus (*Proceedings of the National Academy of Sciences U.S.A.* 108:3011-3016, 2011). This result implies that brain function of children whose mothers had sub-optimal nutrition during pregnancy may be altered throughout their lives.
- Establishment of a nonhuman primate model (the common marmoset) that mimics the human disease process of Ebola and other hemorrhagic fevers (*Human Vaccines* 7:667-673, 2011). This new model paves the way for testing vaccines that can prevent these deadly diseases during natural outbreaks in Africa or as a consequence of terrorist acts.
- Advancement of our understanding from research with chimpanzees of the mechanisms by which all individuals are able to clear hepatitis A virus, whereas many are not able to clear hepatitis C virus (*Proceedings of the National Academy of Sciences U.S.A.* 108:11223-11228, 2011). The results of this study may contribute to the design of vaccines and drugs for the prevention and treatment of hepatitis C.
- Identification in human beings of a new gene whose expression level negatively correlates with risk of major depression in Mexican Americans (*Biological Psychiatry* 71:6-14, 2011). This gene is a novel drug target for pharmacotherapeutics designed to treat major depression disorders.

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. Robert Davey, Ph.D., appointed to the department in July 2011 as Scientist and Ewing Halsell Scholar, was awarded a five-year, $2.5 million contract from the Defense Threat Reduction Agency to use a novel high throughput technology to identify therapies to treat infection with deadly pathogens. 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.

"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."

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 of specific diseases 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 and osteoporosis. The department's population genetic studies of complex diseases are conducted with a variety of U.S. population groups, including Mexican Americans, American Indians and Alaskan Natives, as well as with defined populations in developing countries, including Brazil and Nepal, among others.

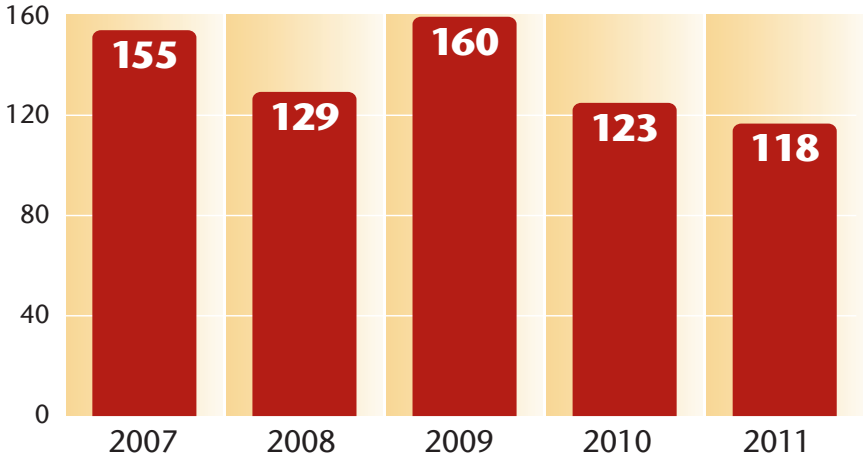
While many of the research projects based in the two Texas Biomed departments are collaborations with the Southwest National Primate Research Center, scientists based in the primate center also have leadership roles in research on cardiovascular disease and on the effects of maternal nutrition on fetal development in the pedigreed baboons; in testing drugs in baboons and monkeys 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, spinal cord injury, and AIDS 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, 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 more than 2,900 nonhuman primates, including chimpanzees and a variety of

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	$13.7	$12.1
Virology & Immunology	3.8	9.0
SNPRC	13.4	19.9
Subtotal	30.9	41.0
Philanthropic	1.1	0.9
Total	**$32.0**	**$41.9**

Number of Texas Biomed Publications by Year



monkey species. 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 multi-year grants awarded during 2011 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 $2.5 million award to Davey, Robert Lanford, Ph.D., in the Department of Virology and Immunology received a $2.3 million grant for research on hepatitis C using the marmoset as a model; and Jean Patterson, Ph.D., and Ricardo Carrion, Ph.D., were awarded grants of $2.7 million and of $1.7 million to develop vaccines against the hemorrhagic fever viruses.

In the Department of Genetics, Timothy Anderson, Ph.D., was awarded a $3.5 million grant to identify genes that confer drug resistance to the parasite that causes malaria and a $1.8 million grant to identify genes that affect the host specificity of the parasite that causes schistosomiasis, which is a chronic illness that causes organ damage. Lorena Havill, Ph.D., received a $3.4 million grant to develop a better understanding of genetics of bone physiology in relation to skeleton diseases. Jack Kent, Ph.D., received a $1.6 million grant to identify genes that cause differential risk of kidney damage in people with long-term diabetes.

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

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Department of Genetics

Ongoing research at the Department of Genetics focuses on the influence of genetic and environmental factors on heart disease, obesity, diabetes, psychiatric disease, parasitic infections, and osteoporosis. Researchers are also undertaking important work on the monogenic disorder cystinosis.

Departmental scientists made major strides in advancing knowledge of the genetic determinants of complex diseases in 2011. This progress was documented in 90 publications in the scientific literature and resulted in over $16.3 million in grant funding received during 2011. Despite the poor funding climate at the National Institutes of Health (NIH), Texas Biomed geneticists received six new major grant awards from NIH during 2011. Research in infectious disease genetics expanded significantly with two new NIH grants awarded to Tim Anderson, Ph.D. Anderson received support to find genes that are involved in resistance to artemisinin combination therapies, the primary treatments used for malaria caused by *Plasmodium falciparum*. His second grant was a new award to support research on schistosomiasis, one of the most significant parasitic infections in the developing world today. This novel project will characterize genes in schistosome parasites that influence snail-host specificity, and the development of the parasites within the snails that are critical to the schistosome life cycle.

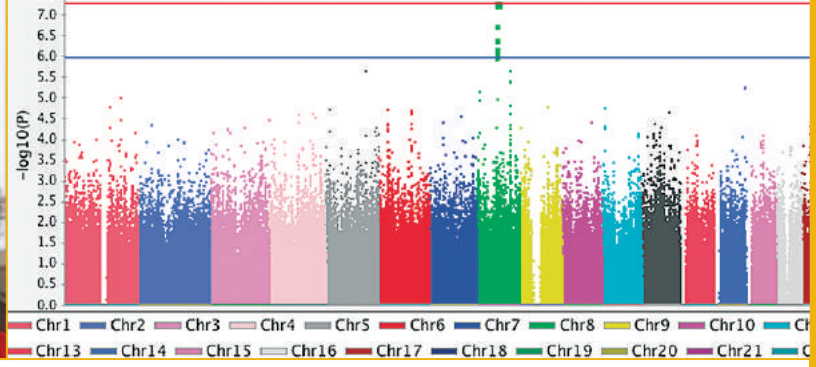
The Department has a major focus on psychiatric disease genetics, and this area of research was enhanced with a new NIH award to Harald Göring, Ph.D., for an innovative project that uses high-throughput gene expression analysis to identify the genes responsive to dopamine that influence risk of schizophrenia. Research on osteoporosis, another complex disease of great public health importance, benefited from a new NIH award to Lorena Havill, Ph.D., to support her study of genetic influences on bone structure and biomechanics in the baboon model. Expanding the Department's research focus on diabetes, Jack Kent, Ph.D., received a new NIH grant to support his research focused on identifying genes involved in pathological response of the kidneys to the high glucose levels in diabetes.

In addition, Eli Lilly & Company granted a major award that affects multiple programs in the Department of Genetics. This project will identify novel drug targets using a unique genetic approach. Deep sequencing of exomes in large Mexican American pedigrees will be used to identify rare protein coding mutations influencing lipid levels. The resulting exome sequencing data will be invaluable for numerous projects within the Department that are based on data from the Mexican American families.

Department scientists had a number of important papers published during 2011. Melanie Carless, Ph.D., and colleagues published results demonstrating that a gene previously identified as a schizophrenia risk gene also affects brain anatomy. Rohina Rubicz, Ph.D., and Harald Göring showed that human susceptibility to many common pathogens, including both viral and bacterial agents, is significantly heritable.

In a paper based on data collected as part of the long-term study of heart disease in Alaskan Eskimos, Saroja Voruganti, Ph.D., Tony Comuzzie, Ph.D., and colleagues demonstrated that QTL influencing adiposity-related traits exhibited evidence of genotype-by-sex interaction. In a major breakthrough for the cystinosis research project, Katy Freed, Ph.D., John Blangero, Ph.D., and colleagues showed that three genes are disrupted in the common form of monogenic cystinosis. Previously, it had been thought that only two genes were disrupted in this devastating disease. This paper demonstrates that the primary disease-causing deletion also alters the *TRPV1* gene. Interestingly, the newly implicated *TRPV1* gene may be responsible for the common observation in cystinosis patients of reduced sensitivity to the heat in chili peppers.

Research results also were presented in numerous talks, lectures and seminars presented by Texas Biomed geneticists at scientific meetings, and at research and educational institutions across the globe. These interactions with the scientific community furthered the international recognition of the Department for its work in the field of complex disease genetics, and led to the development of new research collaborations.



"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 localize and identify genes influencing common, complex disorders and related risk factors."

Laura Almasy, Ph.D.

Scientist, Genetics

Almasy's research examines the roles 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, thrombosis, 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 measures of 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 National Institutes of Health and typically draws 300 or more entries from teams around the globe. Many of the genetic analysis methods currently in use debuted at the workshop. Genetic Analysis Workshop 17, held in 2010, focused on methods for analyzing whole exome sequence data in human cohort or family studies. Planning is now underway for Genetic Analysis Workshop 18, to be held in fall 2012, which will explore methods for analysis of whole genome sequence data.

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

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Staff

Left to right: Philip Melton, Laura Almasy, Mark Kos, 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

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.Anderson's 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.

Anderson's laboratory is using three different strategies to identify genes that underlie resistance. First, they are using genome-wide association methods to systematically search for the genes involved. As the malaria genome is relatively small, they can use whole genome sequence information from populations of parasites to achieve this goal. Second, they are examining the role of copy number variation; already this approach has characterized an important gene involved in drug resistance. Finally, they are selecting resistant parasites in the laboratory and using next-generation sequencing methods to identify the genetic changes that have occurred. Their work involves collaborators in South America, Africa and Southeast Asia.

Schistosomiasis — otherwise known as Bilharzia — 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.

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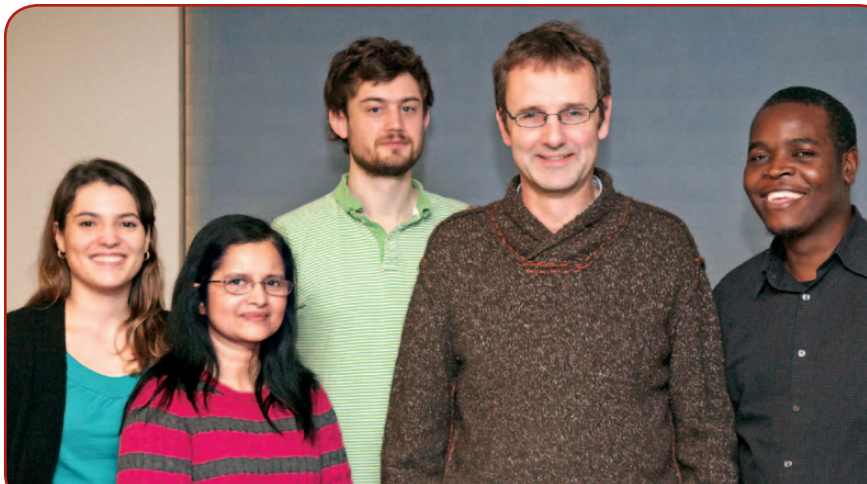
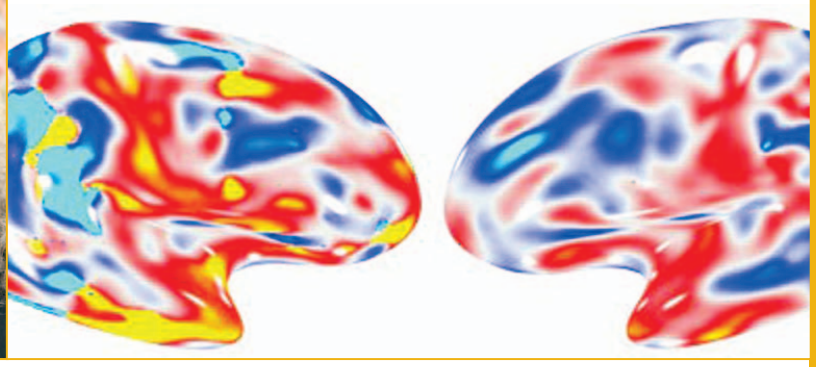
The adult worms live in the blood vessels, but the eggs cause pathology by lodging in the liver or intestine wall, where granulomas form, resulting in periportal fibrosis and hepatosplenic disease. Anderson's work with schistosomes uses a different approach to genetic mapping. He has conducted genetic crosses in the laboratory to generate the first genetic map for a human helminth parasite. This allowed him to assign most of the fragmented genome sequence to individual chromosomes. Anderson and colleagues are now exploiting this map and using linkage mapping methods to identify genes that underlie oxamniquine and praziquantel resistance and other biomedically important traits such as host specificity. The schistosome research involves collaborators at the UT Health Science Center San Antonio, Italy and the UK.

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

Staff

Left to right: Claudia Valentim, Shalini Nair, Ian Cheeseman, Tim Anderson, Standwell Nkhoma





"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 directed a major expansion of resources in 2010 that makes Texas Biomed one of the most powerful genetic analysis centers in the world. Blangero and his research team are recognized as pioneers and leaders in the field of statistical genetics, and they developed a widely used software package for complex genetic analyses. Utilizing the computer ranch, which now has more than 8,000 processors; Medusa; and the advanced high throughput deep-sequencing technology available in the Department of Genetics, Blangero and his colleagues are revolutionizing the search for disease genes.

In an exciting new project, Blangero's lab is undertaking whole genome sequencing for participants in the San Antonio Family Heart Study, a research program begun in 1991 that involves volunteers from 40 extended Mexican American families in the San Antonio area. Many of these people also are involved in a more recent study, the Genetics of Brain Structure and Function Study, or GOBS. Blangero is a principal investigator for both projects, which are searching for genes related to obesity, diabetes, heart disease and kidney disorders as well as genes that regulate the development and function of the brain. Whole-genome sequencing, coupled with the analytical power of the expanded computing center, sets the stage for major advances in the understanding of how genes and environmental factors interact to cause complex diseases. Scientists expect discoveries that can move quickly to translational research and lead to improved diagnostics and treatments for major diseases that impact people around the globe.

This is a period of rapid disease gene discovery. In 2011, Blangero and his colleagues working on the GOBS study identified a new gene related to depression. Using a novel analytical approach, they analyzed 11,000 endophenotypes for their relationships with major depression and found disease risk correlated strongly with expression levels of the RNF123 gene, a neuron growth regulator. This novel gene's expression level now represents a potential biomarker that may prove helpful in identifying people most at risk for major depression.

Aiding the movement toward translational research, Blangero's team recently began a new collaboration with the pharmaceutical company Eli Lilly to generate novel drug targets for the prevention of cardiovascular disease.

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

Publications

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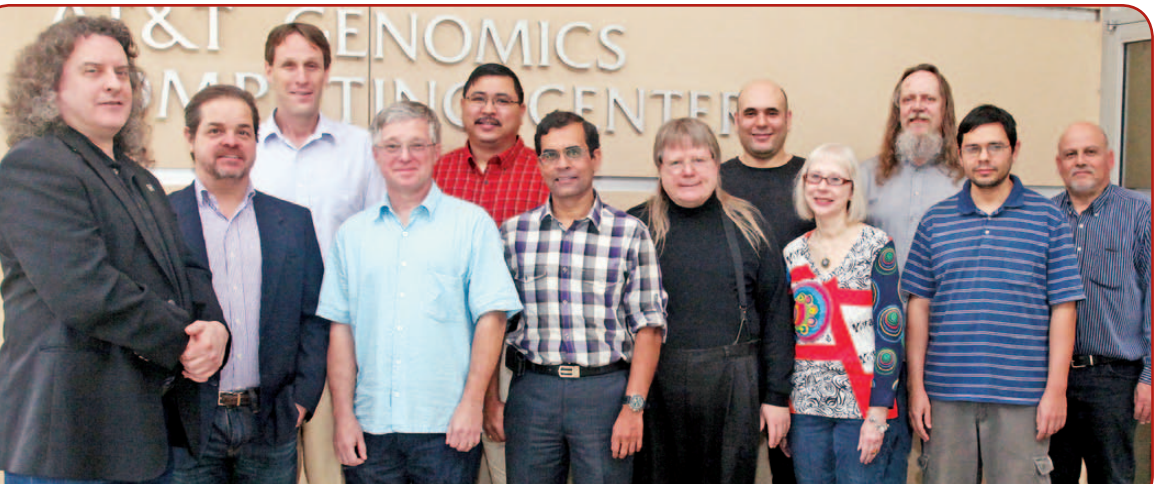
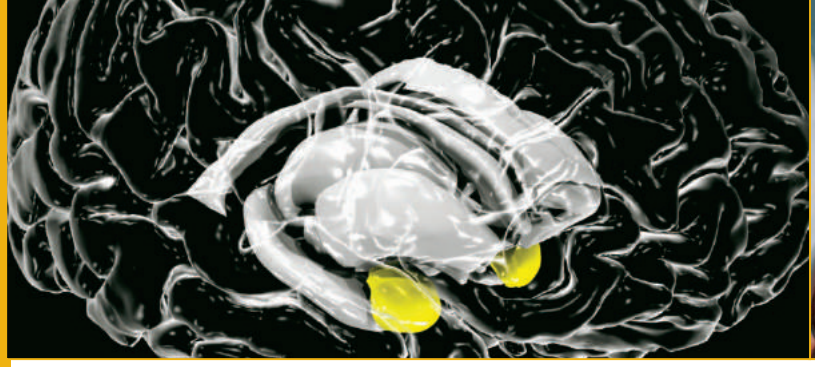


Staff

Left to right: John Blangero, Roy Garcia, Gerry Vest, Jack Kent, Vince Diego, Hemant Kulkarni, Charles Peterson, Marcio Almeida, Linda Freeman-Shade, Tom Dyer, Juan Peralta, Richard Polich



"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.

Assistant Scientist, Genetics

Although researchers are beginning to make progress in understanding the biological mechanisms that drive complex disease development, many areas of study are only just starting to be explored. Epigenetic mechanisms, such as genomic 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 regulate gene expression to influence variation in neuroanatomical and neurocognitive endophenotypes, and how this variation might play a role in psychiatric disorders. Recently, her laboratory has identified several microRNAs whose expressions are both heritable and appear to influence neuroanatomical traits associated with depression. In addition, Carless and her colleagues have uncovered evidence that genomic methylation within a number of genes is correlated with many metabolic syndrome-related phenotypes, such as measures of obesity, blood pressure and insulin and glucose levels; as well as with neuroanatomical and neurocognitive traits. Carless has also continued to assess the role of genetic variation in depression and neurological traits, identifying several variants within an important psychiatric-related gene that contribute to differences in neuroanatomical and neurocognitive traits.

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. 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.

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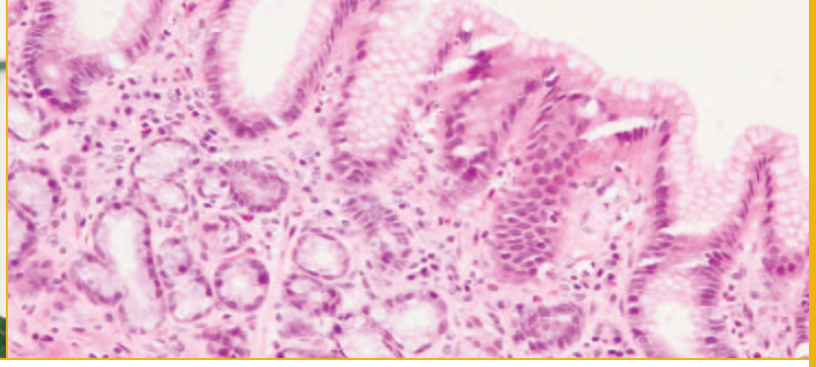
Staff

Left to right: Jennifer Neary, Sarah Heltzel, Melanie Carless, Hemant Kulkarni, Kara Peterson, Jessica Valdez



"Increasingly we are looking at a broader spectrum of complex diseases associated with obesity. We can't study obesity in isolation; 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. 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 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.

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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.

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 have 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 obesity.

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Staff

Left to right: Sandy Laston, Vicki Mattern, Anthony Comuzzie, Saroja Voruganti, 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. Identification and understanding of the mechanisms by which these networks are regulated will provide RNA-based therapeutic targets for prevention of atherosclerosis."

Laura Cox, Ph.D.

Associate 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 variations in response to diet and in response to the maternal environment that influence the atherosclerotic process. In previous work Cox and her colleagues constructed a second-generation baboon genome map. Using the baboon linkage map in conjunction with a novel expression array approach, Cox has positionally cloned and characterized a gene that influences HDL-cholesterol.

Furthermore, her team has identified molecular genetic mechanisms by which variation in this gene influences variation in HDL-cholesterol. Her research team is also using new "next generation" sequencing methods and new analytical tools to identify genetic networks that influence LDL-cholesterol and salt-sensitive hypertension. Another area of study in her lab is analysis of 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. Each genetic network and gene variant that is identified will provide potential therapeutic targets for modulation of blood pressure and serum cholesterol.

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

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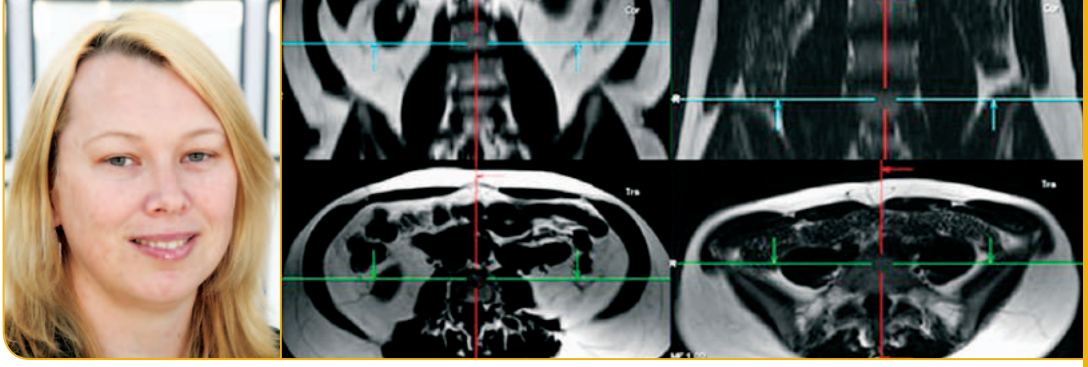
Staff

Left to right: Genesio Karere, Shifra Birnbaum, Jerry Glenn, Laura Cox, Kenneth Lange, Kimberly Spradling, Natalia Kuhn, Clint Christensen



"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 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. She has two ongoing research projects analyzing genes whose expression levels correlate with diabetes and obesity phenotypes. By sequencing, her lab is identifying cis-regulated variants that influence the expression levels of a gene, and then validating results using functional molecular analyses.

A large focus of complex disease genetics is on the importance of rare variants for disease risk. In recent years, her research has changed direction to take advantage of rapidly emerging technologies, and it now focuses on the identification of functional rare variation. Using a combination of next-generation sequencing and the San Antonio Family Study (SAFS) cohort, Curran and colleagues are identifying functional variants influencing diabetes, obesity and heart disease. As part of an NIH funded Type 2 Diabetes Consortium, they are obtaining whole genome sequences for a thousand SAFS members. Additionally, they are performing exome sequencing on other SAFS members in their own studies and in partnership with the pharmaceutical industry. This work will lead to the rapid identification of novel therapeutic targets, and will provide valuable insights into disease pathways and gene interactions within these pathways.

Curran recently obtained internal funds to support a pilot project to investigate the role of the brain and neural networks in obesity, using functional neuroimaging. In the study, subjects will undergo brain imaging (by MRI) and while in the scanner will receive flavored milkshake through a feeding device. Curran will then look for differences in activation of brain regions during receipt of milkshake compared to a tasteless solution. Brain images, combined with whole genome sequence, will be used to identify specific genes and variants that influence the brain's response to food stimulus and obesity.

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 identifying genes influencing the development of heart disease, prediabetes, depression and schizophrenia.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=96**

Publications

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Staff

Left to right: Ram Upadhayay, Iriscilla Ayala, Katherine Truax, Joanne Curran, Grace Ann Arya, Claire Bellis, Santosh Timilsina, Lilliana Paredes, Steven Howard, Cindy Gutierrez

"Genetics, culture and environmental factors interact to influence human health and disease. Using state-of-the-science molecular genetic and statistical genetic tools including the 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 life style factors."

Ravindranath Duggirala, Ph.D.

Scientist, Genetics

With dual interests in anthropological genetics and genetic epidemiology, Duggirala's research group pursues a 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 localize and identify susceptibility genes for complex diseases. For example, they previously localized two genetic regions on chromosome 1p that influence GBD, and now have completed the high-density fine-mapping of these regions to identify the potential functional variants/genes that influence GBD. The preliminary GBD association findings are very promising, and subsequent GBD susceptibility gene discovery activities are in progress. Also, they are currently involved in a collaborative effort to confirm and characterize the genetic associations for T2DM identified from the recent genome-wide association studies as well as to identify additional novel T2DM susceptibility genes in the Mexican American population. As part of this collaboration with colleagues in the T2D-GENES Consortium, they are in the process of generating the whole genome sequence data for 600 individuals from two San Antonio Mexican American Family Studies. In addition, data from several San Antonio Mexican Family Studies are part of the whole exome sequencing project of the T2D-GENES Consortium.

Given the growing epidemic of childhood obesity and its complications, they have examined the precursors of MS in Mexican American children, using the data from the San Antonio Family Assessment of Metabolic Risk Indicators in Youth (SAFARI) Study. Disturbingly, the preliminary data reveal increased prevalence rates of obesity, pre-diabetes, MS, and microalbuminuria among these children.

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

Publications

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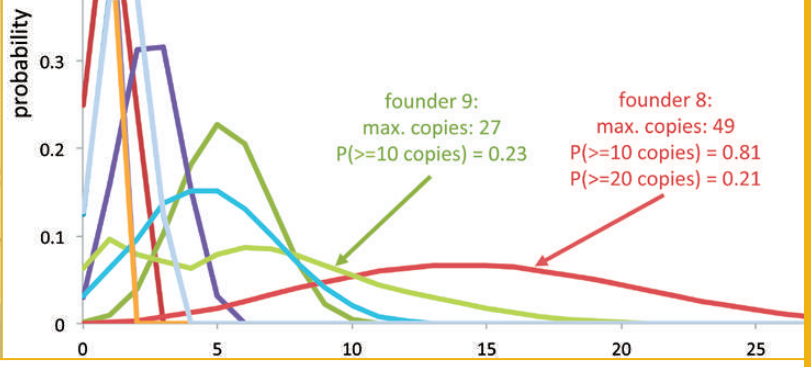
Staff

Left to right: Geetha Chittoor, Valessa Agosto-Cusano, Sharon Fowler, Ravindranath Duggirala, Roy Resendez, Sobha Puppala, Vidya Farook



"We seek to unravel the genetic mysteries behind our human individual characteristics, such as 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 Göring, Ph.D.

Associate 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 their application to well-designed human datasets and novel genomic data.

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

Another 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 from individuals with and without the disease.

Another research topic is the study of common infections, which are now thought to play a hidden role in many diseases not normally considered as infectious diseases (including, among many others, atherosclerosis and perhaps even schizophrenia). Göring's group has measured 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 also may be critical for development of lupus.

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

Publications

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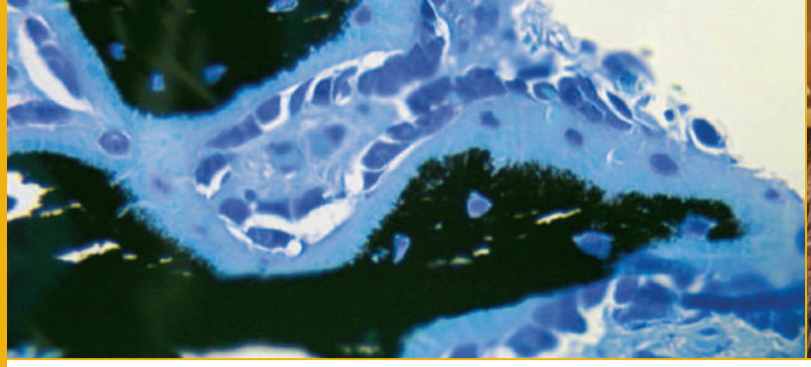
Staff

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



"Osteoporosis and osteoarthritis are public health priorities of immediate concern because of the individual suffering and public health costs associated with these diseases, and because of the alarming rate at which their incidence is increasing as the population ages. My laboratory uses Texas Biomed's baboon colony, ongoing family studies, and computing resources to identify the genes and biological processes that result in high risk of these diseases and that protect from 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 disorders are extremely common age-related skeletal diseases, but their causes, and, consequently, the 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 the pain, stiffness, and limited mobility that make this disease the leading cause of disability in the U.S.

Havill and her team apply molecular and statistical genetic methods in studies of large extended pedigrees of baboons and humans to determine the degree to which genes and sex differences are responsible for variation in traits related to bone fragility and osteoarthritis pathogenesis. Havill studies not only traditional indicators of bone strength (such as bone density) but also more direct measures of bone's resistance to fracture and of variation in joint biomechanics with engineers at the Southwest Research Institute (SwRI), using mechanical testing of bone and joint specimens using the baboon as a nonhuman primate model for human bone and joint health.

Her research program is built on novel study designs to 1) reveal the fundamental biological mechanisms that underlie variation in risk of osteoporosis and osteoarthritis, and 2) identify the specific genes that are most important in disease risk. Her studies involve a holistic rather than reductionist approach to disorders of skeletal aging that she believes is essential to the significant advances in basic knowledge of these disease processes that are required for more effective prevention and treatment.

She and her SwRI collaborator, Dan Nicolella, Ph.D., are developing a "bone structural integrity profile" with the goal of providing a new tool for assessing an individual's risk of bone fracture, a risk that increases with age and the start of osteoporosis. She ultimately hopes to identify individuals who could benefit from early medical intervention to reduce their risk of fracture. In another project, she is studying osteoarthritis of the knee to gain much needed insight into the biological changes that occur in the very early stages of osteoarthritis, before significant joint destruction has occurred and when medical intervention is most likely to be effective. With the addition of postdoctoral fellow, Heather Coan, Ph.D., to her laboratory this past year, Havill is expanding her osteoarthritis research program to address the role of stem cells in osteoarthritis progression.

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

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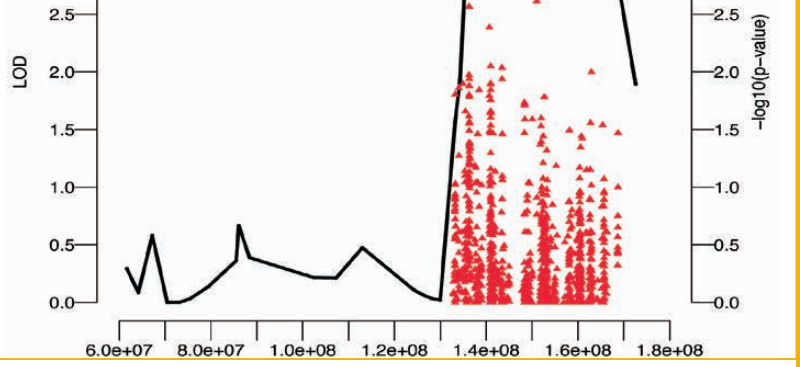
Staff

Left to right: Jennifer Harris, Heather Coan, Lorena Havill, Ahsan Choudary, Shayna Levine



"The rapid advancement of next-generation DNA sequencing technology is providing a powerful tool to elucidate the genetic architecture of common complex disease. Using these technological advances, in combination with powerful computational resources, we aim to identify genes that contribute to preeclampsia susceptibility and several ocular disorders."

Matthew Johnson, Ph.D.

Assistant Scientist, Genetics

Preeclampsia is a common and serious complication of human pregnancy. Irrespective of gestation, delivery of the fetus and placenta is the only effective means to alleviate this condition. Furthermore, preeclampsia is known to increase a woman's risk of later-life cardiovascular disease.

Johnson has had an integral role in the objective identification of several promising preeclampsia candidate regions along chromosome 2q using both family- and population-based study designs. Additionally, he is specifically testing the hypothesis that four aminopeptidase genes residing on chromosome 5q contribute to a woman's preeclampsia susceptibility profile. These four genes have known roles in blood pressure regulation, inflammation, immune response and pregnancy homeostasis, all of which are perturbed in preeclampsia.

Age-related macular degeneration (AMD), glaucoma and diabetic retinopathy are several leading causes of blindness among American adults and all have significant genetic constituents. The identification of novel and the resolution of known genetic factors for these ocular disorders remains a major priority for the development and/or betterment of diagnostic tests prior to the onset of clinical symptoms.

A new collaboration between the Casey Eye Institute in Portland, OR and Texas Biomed has resulted in a recently funded five-year NIH project to resolve known and identify novel AMD genetic susceptibility loci using a joint linkage/association methodology. This project will also reassess the AMD phenotype in a more quantitative manner and use next-generation sequencing technology to sequence the exomes of individuals from numerous AMD families.

Johnson also is actively developing an ocular genetics research program in the San Antonio Family Heart Study (SAFHS) to identify and functionally characterize genes and genetic networks related to AMD, glaucoma and diabetic retinopathy among Mexican Americans. The SAFHS, initially conceived by Texas Biomed Scientists in 1991, now includes more than 1,400 individuals from 42 extended Mexican American families from within the San Antonio area.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=115**

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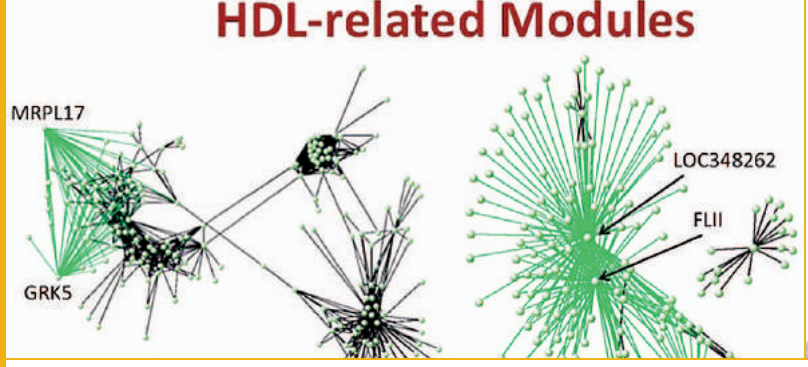

"Each human is a product of billions of reactions on multiple levels of biological organization and interactions between all the levels. Networks of interacting genes provide the blueprints for observed patterns of correlations between clinically relevant phenotypes in health and disease."

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.

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, baboons, and mice, Mahaney and Staff Scientist Magalie Leduc 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. They also have identified networks of genes, often hundreds, which 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. With different sets of bioinformatics tools, he and Staff Scientist Natalia Milshina also have been studying specific classes of mutations likely to affect the ways in which some genes in these networks may simultaneously affect many others and, consequently, our risk for developing cardiovascular disease.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=2**

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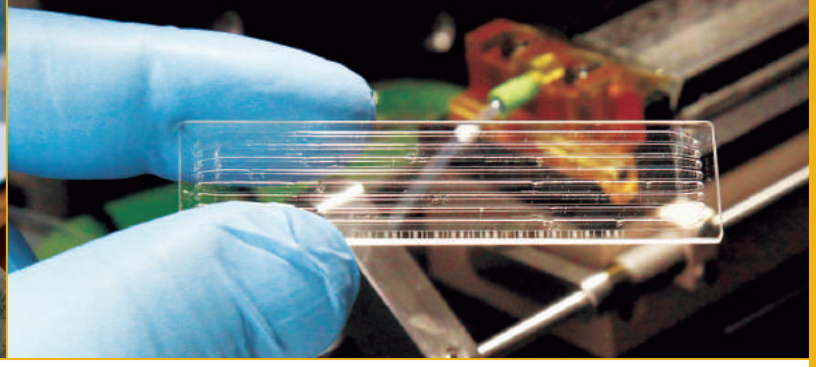
Staff

Left to right: Natalia V. Milshina, Magalie S. Leduc, Michael C. Mahaney



"We are using an integrative genomics approach to uncover the genetic architecture of common human diseases. Our integrative genomics approach is applicable to any common disease (or quantitative phenotype) and is particularly suited to large population family-based studies. We recently demonstrated the power of this approach to study so-called Mendelian single-gene disorders using the rare lysosomal storage disorder cystinosis as an example."

Eric K. Moses, Ph.D.
Scientist, Genetics

Moses and his group are currently studying a cohort of preeclampsia families from Australia and New Zealand. The original genome scan in these families identified a susceptibility locus on chromosome 2 and they have subsequently identified additional susceptibility loci on chromosomes 5q and 13q. In efforts to identify the underlying genetic risk variants at these loci, the team has developed an objective prioritization strategy that combines bioinformatic interrogation, gene-centric SNP genotyping and transcriptional profiling in disease-relevant tissues to generate a priority list of positional candidate genes at each of these three loci.

The team also is integrating high-density genotype data, genome-wide transcriptional profiling data in lymphocytes, deep gene re-sequencing and comprehensive phenotypic data to identify novel candidate cardiovascular disease-related genes. A recent example is the VNN1 gene, whose mRNA expression the group has shown is correlated with HDL-C levels. In a new project, Moses plans to use an integrative approach to identify those genes that are most likely to participate with VNN1 in the global regulatory networks that ultimately play a role in cholesterol metabolism.

In the group's cystinosis research, Moses has initiated an innovative genomic approach to the dissection of a monogenic disease such as cystinosis that avoids the immediate need for large families with individuals affected with the disease. In this strategy, he is employing normal human variation as a model for pathological human variation. In order to determine the larger role of cystinosin, the team has exhaustively enumerated normal human variation in the CTNS gene in a large sample of unaffected families and has tested whether this genetic variation influences the quantitative expression of any other gene (via the measurement of genome-wide gene expression in lymphocytes). Genes that are influenced by causal variation in CTNS become potential targets for pharmacological intervention. Conversely, the group has also used genome-scanning technology to localize novel modifier genes that influence quantitative expression of the CTNS gene. It was argued that for individuals with cystinosis who have incomplete loss of function of cystinosin, 'upstream' trans-acting regulatory genes become possible targets for focused therapeutic intervention aimed ultimately at producing more cystinosin.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=99**

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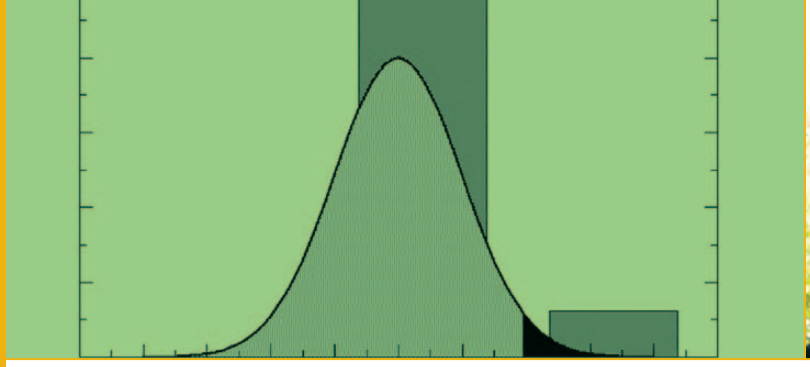

"The primary activity in my laboratory is theoretical statistical genetics and applied statistical computing. The ever-changing nature of genetic data demands a commensurate effort of pure and applied statistical research to develop new models and computational methods for gene discovery and characterization."

Jeff T. Williams, Ph.D.
Associate Scientist, Genetics

Whereas ten years ago statistical models involving one or a few genes were adequate to the task, the immense and complex datasets generated by the current generation of molecular genetic technology are driving the development of novel statistical methods for understanding the dynamics of gene networks and biochemical pathways. Following theoretical investigation, extensive computer simulation studies are generally required to elucidate the properties of competing or alternative statistical methods.

Williams' laboratory is engaged in an ongoing collaborative project to develop the baboon as a nonhuman primate animal model for primary generalized epilepsy in humans. It has been recognized since the mid-1960s that baboons are susceptible to naturally-occurring spontaneous seizures, and exhibit a high prevalence of photosensitive epilepsy.

In this regard the baboon is absolutely unique among the primates: spontaneous seizures are uncommon in other species of monkey and are not observed at all in any of the ape species. The reasons for the unusual sensitivity of the baboon to spontaneous seizures are not yet understood, but the high prevalence of the condition, and its clinical similarity to human juvenile myoclonic epilepsy, make the baboon an exceptional model for understanding the genetics of epilepsy in humans.

Previously Williams directed a comprehensive electroencephalogram evaluation of more than 700 pedigreed baboons from Texas Biomed to characterize the clinical features of their epilepsy. The current research focus is now on adapting conventional neuroimaging modalities, such as functional MRI and perfusion positron-emission tomography, for use with epileptic baboons. The immediate goal is to develop a reliable neuroimaging protocol that can accurately and reproducibly measure changes in cerebral blood flow that occur during seizures.

Williams is also investigating techniques for mapping the spatial (dis)organization of neuronal impulses in the brain during seizures. Ultimately, the development of neuroimaging and neuronal mapping in the baboon will provide the clinical research tools for noninvasive assessment of therapy with antiepileptic drugs.

▶ For more information, please visit **www.txbiomed.org/departments/genetics/genetics-staff-bio?u=56**

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"My research program is focused on the genetic determinants of infectious disease-related characteristics and of traits associated with normal human development. Utilizing statistical genetic approaches and genome-wide scanning techniques, we are assessing the genetic components of a number of parasitic diseases and of aspects of aging in normal individuals."

Sarah Williams-Blangero, Ph.D.

Scientist and Chair, Genetics

Williams-Blangero's investigations of the genetic components underlying susceptibility to parasitic diseases are being pursued in two large-scale human population studies. The soil-transmitted intestinal worm infections (hookworm, roundworm, and whipworm) that affect a quarter of the world's population 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, which is the leading cause of heart disease in Latin America. Williams-Blangero is assessing the genetic components of susceptibility to infection with the parasitic cause *(Trypanomosoma cruzi)* of Chagas disease and of differential cardiac disease progression in individuals who are infected with *T. cruzi*. A major review article published in 2011 summarized the results of the Chagas work to date. The extensive genetic characterization of the human populations involved in these studies of parasitic disease makes them exceptionally valuable for other studies.

Williams-Blangero also has a research program on the genetic factors influencing aging. This study builds on the unique resources generated by the San Antonio Family Heart Study, which has characterized the genetic components of heart disease in approximately 40 large Mexican American families over the last 20 years. Utilizing the transcriptional profiles that have been generated for the Mexican American population, she and her colleagues have identified over 4,000 gene transcripts that are significantly correlated with chronological age. While most transcript levels show a decrease with age, 43 percent of these transcripts show an increase in transcription with age.

Clearly, not all research questions can be answered by studies of humans. Through work with the Southwest National Primate Research Center and the Caribbean Primate Research Center, Williams-Blangero continues to pursue an interest in genetic management of nonhuman primate colonies.

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

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Staff

Left to right: Sarah Williams-Blangero, Cheryl G. Raindl

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 so as 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.

Texas Biomed virologists have two advantages in their research. The department's state-of-the-art facilities include the nation's only privately owned biosafety level four (BSL-4) maximum containment laboratory. This facility — which has proven especially beneficial in support of the nation's biodefense efforts — allows scientists to safely study the most lethal pathogens for which there is no known treatment or cure.

Also extremely valuable are the availability of Southwest National Primate Research Center's nonhuman primates. These animals offer the most effective models for human infectious disease, as well as for the evaluation of therapeutic drugs and vaccines against viral agents.

Talented scientists, coupled with these extraordinary resources, have enabled the department to report $6,438,744 in total grants and contracts in 2011, the largest amount in departmental history. Not only were a record number of new grants awarded, but researchers also submitted proposals totaling over $58,025,238 million to various funding agencies.

The department hired Robert Davey, Ph.D., as its first Ewing Halsell Scholar. Davey did his doctoral work in Australia, moved to Harvard Medical School and then to UTMB. His goal is to identify new drugs that can be used to combat high-containment pathogens. Drugs are particularly effective for short- to mid-term protection or when people are in areas where a recent outbreak has occurred or vaccination is not possible. The BSL-4 maximum containment laboratory in the Department of Virology and Immunology offers the perfect environment to develop and optimize an alternative workflow for identification of drugs for high containment pathogens. He and his colleagues have developed semi-automated approaches to drug screening that are safe, efficient and work at high containment.

Robert Lanford, Ph.D., has shown that a new drug stimulates the immune system by binding Toll-Like Receptor 7 and provides new hope for the 350 million people chronically infected with hepatitis B virus (HBV). In collaboration with Gilead Sciences, the Lanford lab demonstrated that the drug suppresses the virus by more than 600-fold in HBV-infected chimpanzees. Importantly, the suppression of virus levels lasts for months after the end of therapy.

The laboratory of Luis Giavedoni, Ph.D., has identified that certain local inflammatory diseases can affect AIDS disease outcome. Specifically, Giavedoni's lab and collaborators have seen that local inflammation of the gums does not increase the risk of acquiring infection with SIV by the oral route; however, in this monkey model of HIV infection, animals that had gingivitis and became infected with SIV developed increased systemic inflammation compared with infected animal without gum disease. The systemic inflammation may lead to a more rapid progression to AIDS.

Kris Murthy, Ph.D., is continuing his work on developing and testing of the AIDS virus. Rebeca Rico-Hesse, Ph.D., is continuing to develop an animal model to predict pathogenicity of dengue virus infections.

The central goal of the lab of Andrew Hayhurst, Ph.D., is to develop a reliable system for producing stop-gap antigen capture assays to any given pathogen, toxin or biological marker in a single day, to offer a rapid diagnostic response to containing novel biothreats. As part of this, a simple scheme uses llama single domain antibodies to be isolated, screened and paired to forumulate immunoassays within a handful of days. This novel pipeline has been filed as a provisional patent application.

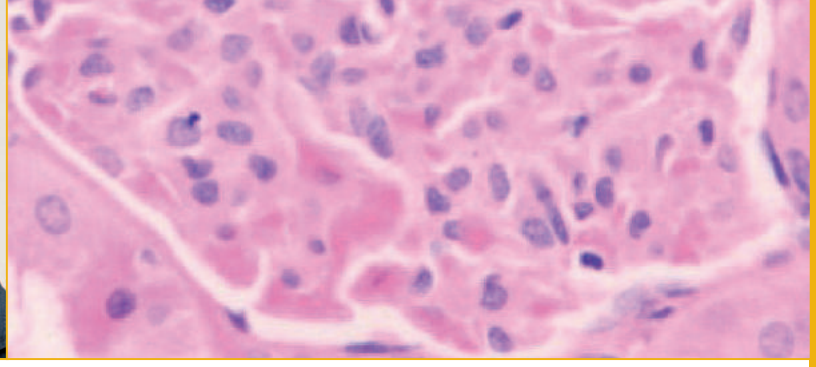
Ricardo Carrion, Ph.D., has pioneered the use of the marmoset as a non-human primate for animal disease. He and his colleagues have recently published data supporting the use of the common marmoset as a model for Ebola and Marburg hemorrhagic fever. The marmoset is a small non-human primate weighing less than a pound and is especially well suited for work in high containment. They have shown that a single intramuscular injection of as little as 10 pfu of virus causes a disease that closely mimics human disease.

The lab of Anthony Griffiths, Ph.D., works to understand how viruses that normally infect animals can jump into humans. Much of the lab's work has focused on herpes B virus, which is the monkey equivalent of herpes simplex virus (cold sores in humans) and the two viruses are similar in many ways. However, herpes B virus causes a very minor disease in macaque monkeys but is frequently fatal to humans who become infected. The Griffiths laboratory is at the forefront of the interface between viruses and microRNAs, which are molecular switches that serve to control the levels of specific proteins in cells. Griffiths and his colleagues believe that microRNAs are important for herpes B virus disease, particularly for the differences in the disease seen in monkeys and humans. Their data represent the most comprehensive analysis of virus-encoded microRNAs to date and will provide the framework for understanding herpes B virus disease in humans. This work has already been the focus of a review article and has been discussed in detail in a second review.

Marie-Claire Gauduin, Ph.D., recently received funding to develop a novel mucosal AIDS vaccine. She and her colleagues had established and optimized the neonatal macaque model to study nasal TB infection in infants. The Gauduin lab is also investigating the kinetics and pathways of viral spread of SIV in macaques by using an SIV tagged with a green fluorescent protein.

The department chair, Jean Patterson, Ph.D., is developing vaccines and therapeutics against Ebola, Marburg and Lassa fevers. With graduate student Jesus Alonso, they are showing how two strains of Marburg virus exhibit different lethality rates in humans. She is also continuing her work on the pathogenesis of leishmaniasis, a serious parasitic disease of the tropics.

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 viruses representing several distinct families of viruses, many of which 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 SFBR'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. Identification of a small nonhuman primate model for filovirus disease of the size of rodents is important as they are more predictive of therapeutic efficacy than traditional small animal models.

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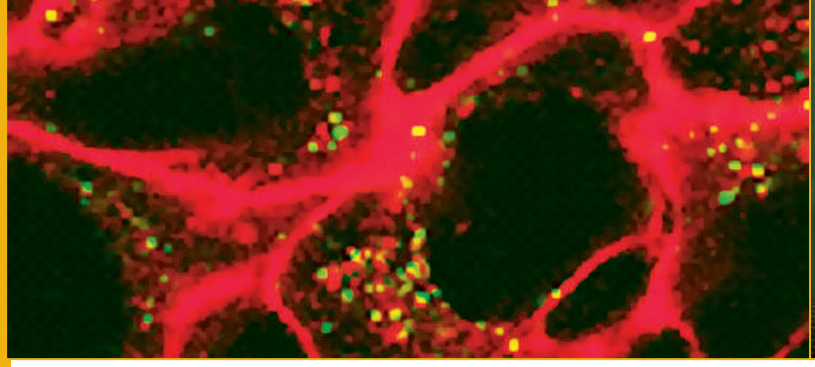
The second focus of Carrion's research is development of candidate vaccines for hemorrhagic fever. Most recently Carrion and his colleagues have been awarded contracts to test the efficacy of several vaccine platforms against filoviruses. Vaccines being tested by Carrion's team include multivalent virus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

The third focus of Carrion's research is development of new detection methods for bioterror agents. Most recently Carrion has teamed with a local biotechnology company to test a Handheld Aptamer-Magnetic Bead-Quantum Dot Sensor for Crimean Congo Hemorrhagic Fever (CCHF). CCHF is a tick-borne disease causing hemorrhagic fever in eastern Europe, Asia, India and Africa. Overall fatality in patients hospitalized for the disease ranges from 9 percent to 50 percent.

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

Staff

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



"The fight against viral pathogens is ongoing and we cannot afford to let our guard down. We have dodged a number of bullets just over the last 10 years between naturally evolving and emergent pathogens as well as those made and released intentionally. The problem is that few facilities are capable of handling the type of pathogens that cause severe human disease, let alone to find drugs to combat them, because of the hazard posed to laboratory workers. My goal is to identify new drugs that can be used to combat these pathogens."

Robert A. Davey, Ph.D.
Scientist, Virology and Immunology

Drugs work together with vaccines to protect us against disease. Drugs are particularly effective for short to mid-term protection or when people are in areas where a recent outbreak has occurred or vaccination is not possible. Drug identification in the pharmaceutical industry has relied on testing large sets of chemicals, often in the millions, to block replication of virus or bacterial pathogens. After finding several thousand chemicals that work weakly, organic chemists modify and improve some of them to make more effective compounds and to ensure low toxicity and side effects to the patient. To handle so many chemicals is difficult and relies on robotics and other complex equipment. Unfortunately, this equipment is large, expensive and dangerous and requires continuous maintenance making it impractical to house in the high-containment laboratory.

The BSL-4 maximum containment laboratory in the department of Virology and Immunology offers the perfect environment to develop and optimize an alternative workflow for identification of drugs for high containment pathogens. We have developed semi-automated approaches to drug screening that are safe, efficient and work at high containment. These include a microscope system that can automatically take photos of infected cells in 96 and 384-well plates as well as computer software that we have customized to automatically identify infected cells and determine drug efficacy. To ensure safety, our lab personnel are still heavily involved in hands on work but we can drastically reduce the time to finding effective drugs by 90 percent over more traditional methods by using this approach. Still, testing millions of chemicals would take a very long time but we have developed systems that can be used at low containment to help narrow down targets to a few thousand chemicals which can be tested in a few weeks. Presently we are engaged in an ongoing project with a major drug screening facility at the National Institutes of Health. Our goal of this project is to identify new drugs against Marburg (cousin of Ebola virus) and Lassa fever viruses. The hits from this screen will be testing and optimized in the BSL-4 lab at Texas Biomedical Research Institute. We are also working with other labs in the department to help analysis of data and assays and are already reaping the benefits in time and cost savings.

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

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Staff

Left to right: Manu Anantpadma, Janelle Bentz, Robert Davey, Robert Maldonado, Olena Shtanko

"Our laboratory is focusing on the SIV/macaque model for AIDS to understand the early mechanisms of mucosal HIV/SIV transmission, the generation of cellular and humoral immune responses, the immune correlates to disease progression in adults and infants, the immunopathogenesis of HIV/TB coinfection in pediatric AIDS, and the development of novel vaccine strategies."

Marie-Claire Gauduin, Ph.D.

Assistant Scientist, Virology and Immunology

Gauduin's laboratory is investigating the early events of SIV transmission in macaque 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.

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 non-pathogenic 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.

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.

TB 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 established an experimental acute M. tuberculosis infection in the newborn primate model to produce progressive and/or active but asymptomatic infections that mimic the clinical and pathologic effects of pediatric tuberculosis. The ultimate goal is to optimize neonatal primate model for TB/HIV co-infection to study immunopathogenesis of TB/SIV interactions, the impact of treatment and treatment interruption on the evolution of tuberculosis.

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

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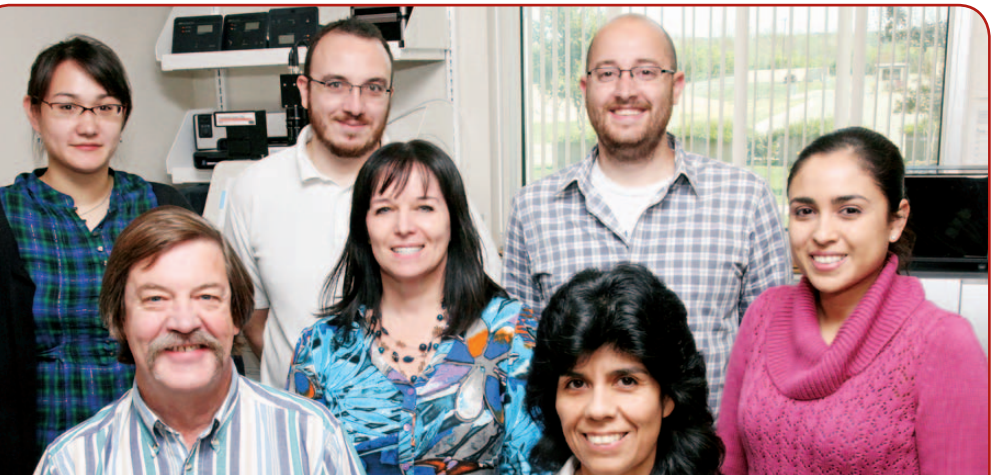
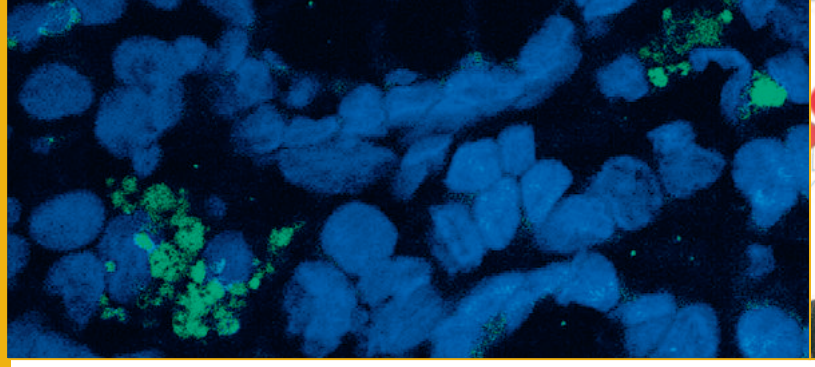


Staff

Left to right: Jessica Folwarczny, Robert (Bobby) White, Gregory Bonello, Marie-Claire Gauduin, Peter Lentz, Mary Salas, Magdalena Cepeda



"My principal research interests include the study of viral infections and the development of novel vaccine approaches against such infections, with special emphasis on understanding the innate and adaptive immune responses to retroviral infections in animal models."

Luis Giavedoni, Ph.D.

Scientist, Virology and Immunology

In Giavedoni's laboratory, particular attention is given to the role and function of cytokines, molecules that mediate communication between the immune system and the whole organism. His research group has been developing technology for the identification of cytokines in nonhuman primates and also studying the potential use of these molecules to modify the outcome of immune responses.

Ongoing projects in AIDS vaccine development in Giavedoni's laboratory use the rhesus macaque/simian immunodeficiency virus (SIV) model. One such collaborative project includes the use of nanoparticle technology to deliver SIV genetic material to mucosal surfaces of the macaques. This vaccination was able to prime the immune system so that animals reacted with stronger immune responses when they were boosted with a second vaccine that consisted of a viral vector expressing the same genetic material included in the first vaccine. When the vaccinated monkeys were exposed to an infectious SIV, half of the animals resisted infection. These very encouraging results will be repeated in a larger and more controlled study.

Another AIDS-related project also involves nanoparticle technology, but in this case the particles carry small nucleic acids that are designed to bind and inactivate the viral genome within infected cells. Giavedoni's laboratory has identified four different molecules that can inhibit SIV replication, which would reduce the chances for viral escape.

A third project involves the creation of novel vaccines based in chimeric proteins that can simultaneously induce and stimulate an immune response. These chimeric proteins are composed of one of the SIV glycoproteins fused to a protein used by cells of the immune system to increase antibody production. A couple of these chimeric proteins have been shown to have the capacity to stimulate macaque cells.

In collaboration with scientists from the Department of Genetics, Giavedoni's lab is trying to identify the mechanisms that allow certain monkey species to resist natural infection with SIV; it is believed that understanding these mechanisms may lead to new therapeutics treatments for HIV-infected individuals.

Finally, the Immunology Core Laboratory of the Southwest National Primate Research Center, led by Giavedoni, also supports other investigators by providing flow cytometry, luminex, and genotyping assays for several nonhuman primate species. It also participates in the National Institutes of Health Nonhuman Primate Reagent Resource. All these services have provided critical help to scientists who perform research with nonhuman primates at the SNPRC.

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

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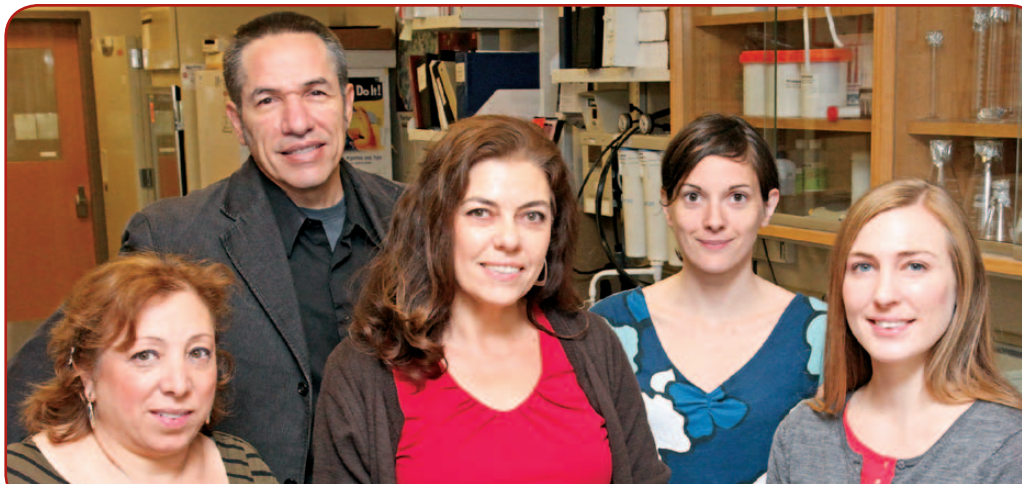
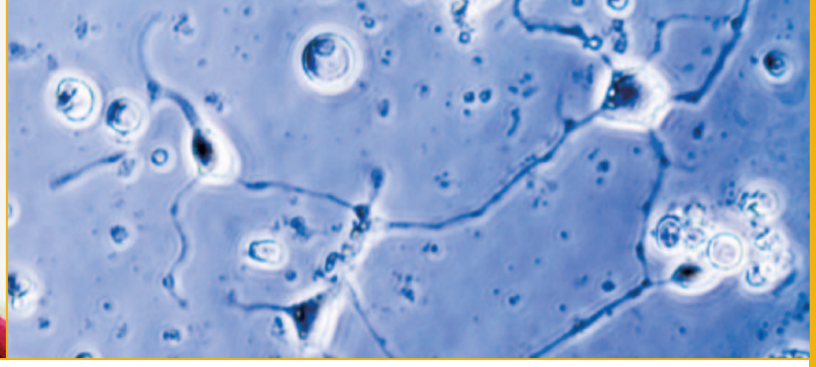
Staff

Left to right: Vida L. Hodara, Luis Giavedoni, Laura M. Parodi, Valerie Sexton, Lisa M. Smith





"One of our long term goals is to understand how viruses jump between species. Our studies of herpes B virus, a virus that naturally infects monkeys but is deadly when it infects humans, are revealing novel mechanisms used by viruses to interact with cells. Identification of these factors will help us predict the next emerging infectious disease and lead to new approaches to treat viral diseases."

Anthony Griffiths, Ph.D.

Assistant Scientist, Virology and Immunology

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. In monkeys, herpes B virus causes a minor self-limiting disease. In dramatic contrast, human infection with herpes B virus frequently causes a severe brain infection (encephalitis) that is typically fatal. Emerging diseases frequently arise when a virus jumps into a new species. Therefore, understanding how herpes B virus jumps between species may provide important clues that will help predict future emerging diseases.

Due to the 80 percent mortality rate in infected humans, herpes B virus may only be propagated in a Biosafety Level-4 laboratory such as we have at Texas Biomedical Research Institute. This, in combination with the large number of macaques housed at the SNPRC, means that we are uniquely positioned to study this important pathogen. Griffiths' laboratory studies the molecular mechanisms that cause herpes B virus to be deadly in humans but relatively benign in monkeys. They have been focusing on a newly recognized class of molecules known as microRNAs, which are encoded by some viruses and appear important for pathogenesis. In 2011, Griffiths' laboratory published a study in the *Journal of Virology* that used next-generation sequencing technology to discover herpes B virus-encoded microRNAs. Using this information, they investigated how these microRNAs were expressed, including studies using monkey tissues. This was the first in-depth study of viral microRNA expression and resulted in some interesting and surprising discoveries, including the first observation that microRNAs are incorporated into the virus particle.

His laboratory is expanding their studies of herpes B virus molecular biology into surveillance by asking whether people who frequently come into very close contact with macaque monkeys have an increased likelihood of herpes B virus infection and disease. For this project, they have teamed with veterinarians from EcoHealth Alliance, who are interested in the intricate relationships between wildlife, ecosystems, and humans. With EcoHealth Alliance they are beginning to investigate the cause of unexplained brain infections in Malaysia and Bangladesh. Additionally, they are trying to determine the frequency of herpes B virus exposure by testing the prevalence of herpes B virus antibodies in monkeys and humans.

Although a major goal of their research is to improve the safety of animal care staff who work with macaque monkeys, much of their work has major implications for studies of other viruses.

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

Publications

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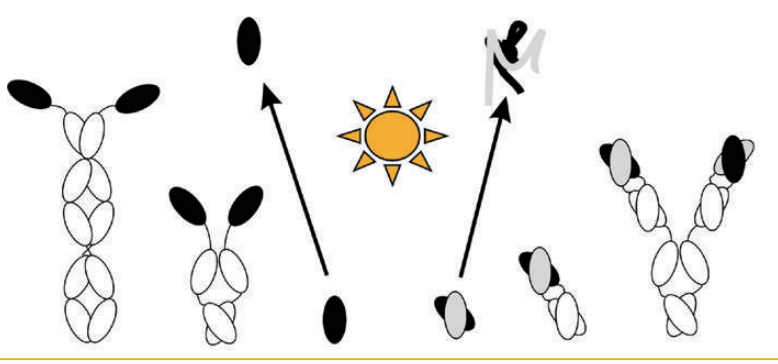
Staff

Left to right: Kendra Alfson, Bethany Brooks, Anthony Griffiths, Melanie Amen



"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 that can be immediately utilized in stop-gap detection kits, enabling us to respond to novel threats within days instead of months."

Andrew Hayhurst, Ph.D.

Associate Scientist, Virology and Immunology

The spectrum of operating conditions under which field portable diagnostics and detection systems are used in the field is enormous. The harshest conditions are usually found in resource-poor areas of the world where electricity and refrigeration are rare, and re-supply is difficult. Such areas require extremely rugged yet simple-to-operate single-use (dipstick) systems with long shelf-lives. Harsh conditions also exist on the homeland front due to the need for constant real-time environmental monitoring of biothreats in multiplex. A highly promising antibody format with the potential to solve these problems is the single-domain antibody (sdAb or nanobody).

Hayhurst's team has generated sdAb specific for Marburgvirus and Ebolaviruses which are highly lethal African hemorrhagic fever viruses sporadically yet explosively emerging and also are Centers for Disease Control "bioterror" threats. The sdAb appear to approach the sensitivity of current detection systems, yet are refoldable and therefore more stable. Hayhurst's team is currently using in vitro evolution within a novel selection and screening system he recently invented to further improve the limits of detection of these antibodies to enable a practical dipstick assay to be developed for these infections.

Another group of 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 recently succeeded in engineering a heptaplex assay for the seven known serotypes based upon sdAb, all of which are refoldable and suitable for use in a rugged multiplex biosensor platform.

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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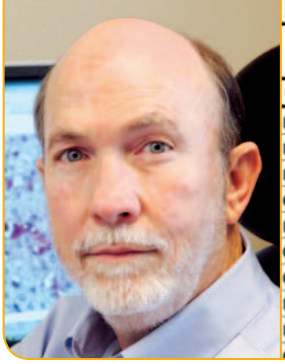
Staff

Left to right: Laura Sherwood, Divya Nandamudi, Andrew Hayhurst, Sena Rayos



Weeks Post Infection	HAV Acute Infection 4x0395								HCV Acute Ch1			HCV Acute Ch2			
Gene Symbol	1	2	3	4	6	10	14	26	2	4	8	3	4	6	8
ISG15	3	4	3	3					36	65	78	11	18	23	17
IFIT1		4							26	21	19	6	11	10	8
IFI6		3	3						21	23	24	10	11	13	10
OAS2		3	3	3					8	6	5		9	6	6
IFIT3		4	3						36	32	42	5	8	11	9
OAS1									24	11	13	4	7	5	6
OAS3		3							47	36	29		6		8
MX1		3	3	2					19	20	17	5	6	8	7
IFI44									18	19	21	3	6	5	5
OAS1									22	17	19	4	5	6	5

"The best approach to preventing hepatitis disease progression and cancer is to cure the viral infection. We are performing the last stage of preclinical testing on new treatments for hepatitis prior to their use in human trials and many of these therapies involve novel approaches that are applicable to other human diseases."

Robert Lanford, Ph.D.

Scientist, Virology and Immunology

The laboratory of Robert Lanford is involved in three research programs involving hepatitis B virus (HBV), hepatitis C virus (HCV) and GBV-B, a surrogate model for HCV.

One of the primary focuses of Lanford's research program is to better understand the interactions of the hepatitis virus with the host, and how it influences either viral clearance or persistence and disease progression. The chimpanzee is the only animal other than man susceptible to infection with HCV, thus Lanford has studied this animal model extensively. Using DNA microarray technology, his team currently examines liver tissue from HCV-infected chimpanzees for changes in expression due to viral replication of 47,000 genes and the immune response to viral infection. Within days of infection, hundreds of interferon response genes are increased in expression in the liver. Although the virus manages to persist in the liver, the host limits the spread of the virus such that only a minor fraction of hepatocytes are infected. The data suggest that the mechanism of viral clearance during a successful immune response is dependent on both the innate and adaptive T cell response. In a multi-institute collaboration, Lanford recently compared the immune response to HCV and hepatitis A virus (HAV), a virus with many similarities to HCV, but differs in that it never induces chronic infection. Remarkably, they discovered that during HAV infections little to no induction of interferon response genes occurs in the liver (Fig). 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. 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.

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Another goal of his HCV 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, many of which have progressed to phase I and II clinical trials. Recent data demonstrate that new antiviral cocktails currently in clinic trials offer a cure of HCV chronic infection without the harsh side effects of interferon therapy.

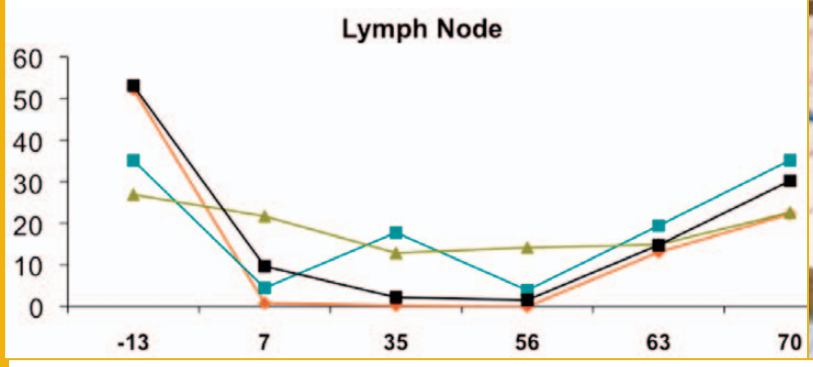
One of the antivirals examined by Lanford sequesters a liver-specific microRNA, miR-122, that is essential for HCV persistence. The drug SPC3649 (Miravirsen in the clinic) was developed by the Danish company Santaris Pharma and is an antisense oligonucleotide that targets miR122. This drug is the first example of a DNA-based therapy that is highly efficacious when administered systemically.

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

Staff

Left to right: Robert Lanford, Deborah Chavez, Lena Notvall-Elkey, Bernadette Guerra, Helen Lee, Henry Bautista, Laura Avena

Not shown: Evet Perez



"A major focus of our laboratory is to identify immune correlates of protection in order to develop better vaccines against infectious agents that cause acute or chronic diseases in humans."

Krishna K. Murthy, D.V.M., Ph.D.

Scientist, Virology and Immunology

Murthy's group has taken an "outside the box" approach to designing and developing novel vaccine strategies for prevention of HIV infection. Under optimal experimental conditions, both passively administered or actively induced antibodies prevent infection with HIV. Those studies have resulted in the identification of a monoclonal antibody that blocks the HIV-receptor complex on CD4+ target cells and prevents infection with HIV both in vitro and in vivo. Additional studies have led to the identification of conserved binding site of the antibodies in the receptor complex, its amino acid composition, and creation of synthetic peptide vaccines. In preliminary animal studies, the synthetic peptide vaccine has been shown to induce antibodies with similar biological activity as that of the monoclonal antibody. This vaccine approach has completed additional safety and immunogenicity studies in nonhuman primates. Plans are underway to vaccinate additional groups of rhesus monkeys to determine the efficacy of the vaccine in preventing infection.

Another novel vaccine strategy being pursued is the use of an envelope protein from a virus known as GBV-C and unrelated to HIV, as a vaccine to induce both antibody and T cells responses to prevent infection with HIV. GBV-C is prevalent in approximately 1 percent of blood donors in the US and does not cause any disease in humans. Co-exposure to both GBV-C and HIV results in protection of CD4 cell numbers, delayed progression to disease, and decreased mortality due to AIDS. Additional in vitro studies show that the protection is mediated by antibodies specific to the envelope protein of GBV-C. Such antibodies neutralize infection by genetic variants of HIV suggesting that the protection mediated by them is quite broad. In a pilot study, rhesus monkeys were immunized with the recombinant E2 protein derived from GBV-C and the vaccinated monkeys developed antibodies that neutralized a panel of HIV-1 isolates in vitro. Plans are underway to challenge the monkeys with a infectious SHIV isolate (a chimeric virus consisting of HIV-1 envelope and SIV genes) to determine the efficacy of the vaccine.

Another exciting vaccine approach is focused on using gp120 covalent analogs as immunogens to selectively induce antibodies to the CD4 binding site (CD4BS), that is absolutely essential for HIV to bind to its target cell. In vitro studies with CD4BS antibodies derived from immunized mice and monkeys have demonstrated that they have potent and broad neutralizing activity against a panel of HIV isolates. Murthy plans to utilize this vaccine strategy along with novel adjuvant formulation to vaccinate rhesus monkeys and challenge with a SHIV isolate by the vaginal route to simulate the major route of transmission of HIV in humans. It is anticipated that the vaccinated monkeys will develop broad and persistent antibody response that will prevent infection or disease progression.

▶ For more information, please visit **www.txbiomed.org/departments/virology/virology-staff-bio?u=32**

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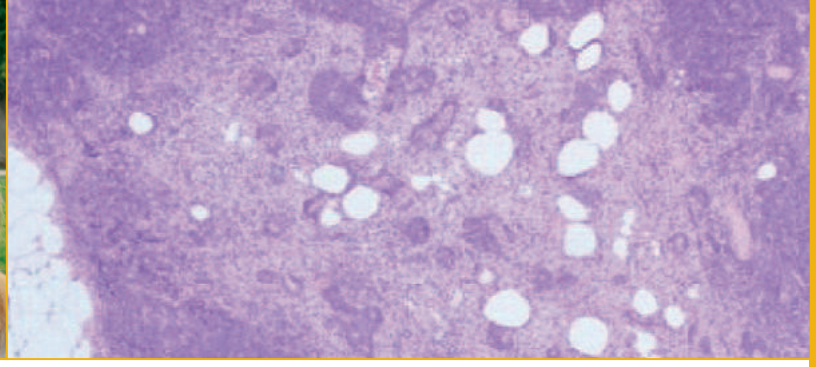

"Texas Biomed's Department of Virology and Immunology develops vaccines and therapeutics against highly lethal viral pathogens, and determines how they replicate and spread through basic and applied research. To defeat viruses that cause AIDS, hepatitis, herpes, hemorrhagic fevers, and a host of other 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. Patterson's laboratory has worked on the development of countermeasures against many select agents. Her group works to develop therapies and vaccines against naturally occurring pathogens that can cause sporadic but lethal outbreaks. She has helped develop three vaccines against Ebola, one with Emory University and one with Crucell pharmaceuticals and one with Bavarian Nordic, all are under going further studies.

The laboratory has also worked with the University of Maryland on the development of two vaccines against Lassa fever. Lassa fever is a hemorrhagic fever that causes serious outbreaks in West Africa; more than 500,000 persons are infected every year with approximately a 10 percent fatality rate and many different forms of lasting effects. The Defense Department 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 assistant scientist in the department, she has developed the marmoset as a model for many infectious agents. The marmoset is a small non-human primate that is not readily available to researchers. Its size and behavior make it a much better model than other larger and more aggressive non-human primates. To date, Carrion and Patterson have utilized the marmoset for the model development of Eastern Equine Encephalitis virus, Lassa fever virus, 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**

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Staff

Left to right: Marsha Sojot, Hillary Staples, Jesus Alonso, Jean Patterson, Marco Rendon

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.

In addition, the SNPRC provides investigators opportunities to select from a wide variety of species to meet their research needs. Large colonies of baboons, macaques, common marmosets, and chimpanzees are available, and our facilities and expertise are appropriate for managing other species that are purchased for investigators when needed.

The SNPRC makes available to genetic researchers the largest pedigreed nonhuman primate population in the world. That pedigree spans six 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 NPRC program and increased ABSL-3 capacity. It has made large numbers of primates of diverse species available as a national resource, and 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 major chimpanzee and 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.

The SNPRC research programs are each assigned to one of three focus groups that bring together all scientists who have shared scientific interests. These focus groups are Infectious Diseases and Biodefense, Chronic Diseases, and Development and Aging. Since each research project is assigned to a single focus group, some investigators belong to more than one focus group. This structure, administered by the Research Resources Branch, 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 (ABSL-4).

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 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. Brasky and her colleagues have developed the expertise to work with a variety of hemorrhagic fever viruses, multidrug resistant bacteria, and various emerging pathogens in both rodent and nonhuman primate models.

Publications

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Staff

Left to right: Joe Vallejo, Mike Diaz, Nancy Martin, Danny Alonzo, Theresa Valverde, Leo Torres, Juan Zapata, Kathleen Brasky, Emmanuel Acheampong, David Pineda, Donna Layne-Colon, Laurie Condel, Robert Geiger, Cassondra Bauer, Melissa de la Garza

"The primate center's Veterinary Resources staff ensures that each animal's living environment is optimal while veterinary research technicians provide the ideal research setting. The center's comprehensive training program is designed to allow animal care and technical staff to advance in their field of expertise and afford opportunities for advancement in laboratory animal care and research. We are committed to providing animals entrusted to us with the most knowledgeable, dedicated, and compassionate animal care possible in biomedical research."

Larry B. Cummins, D.V.M.
Associate Director for Veterinary Resources and Institute Veterinarian

John C. Bernal, D.V.M.
Assistant Director for Veterinary Resources

SNRC 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 inception to accomplishing the final research objective, the veterinary resources team of veterinarians, technicians and support staff aid in study design, in-life study execution, and 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 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 6-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 post-doctoral, are trained by the Veterinary Resources professional staff. Seven veterinarians and two veterinary pathologists are on staff. A six-person Behavioral component within Veterinary Resources provides assistance to the veterinary staff for animal enrichment and training, behavioral modification, and abnormal behavior prevention, in addition to providing research support to investigators.

▶ For more information on Larry Cummins, please visit **www.txbiomed.org/primate-research-center/primate-research-center-staff-bio?u=124**

Staff

Left to right: Wade Hodgson, Christopher Smith, Manuel Aguilar, Michael Washington, Cindy Peters, Brooke Stotler, Bill Cummins, Ty May, John Bernal, Terry Naegelin, Julyne Centeno, Jennifer Diaz, Russell Starr, Jahnni Robinson

"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 this manner is a privilege. Thus their contribution to this endeavor should never be diminished, nor their care compromised. As a laboratory animal veterinarian, it is my responsibility to maintain the highest quality of care for our animal colonies so that we may provide healthy animals to our investigators."

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

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 all research protocols conducted in the laboratory.

Realizing that establishment of animal models is integral to the success of any infectious disease program, a staff of veterinarians, veterinary technicians and pathologists skilled in the care and use of laboratory animals operate the laboratory. Although our facility is equipped to manage all species of laboratory animals less than 10 kilograms, we specialize in the use of nonhuman primates.

By selecting a dedicated core staff of veterinary technicians specifically trained to work with NHPs, the SNPRC staff can assure investigators that each of their animals and protocols will receive uncompromising care and attention to detail. Animals are monitored closely throughout the progression of each study, such that end results will be sound research with unquestionable integrity. 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 develops relationships with each animal, learning their likes, dislikes and individual characteristics. The SNPRC staff feels strongly that the high quality of care for each animal is directly proportional to the high quality science produced. Care provided to the animals is never compromised and is without a doubt the center's most valuable asset.

In the nearly six years that the facility has been operational, the center has conducted a number of vaccine development and animal model studies using both select and non-select agents. Some of these include the use of *Bacillus anthracis* (Ames, Sterne), *Francisella tularensis*, Japanese Encephalitis, West Nile Virus, Dengue(1-4) Virus, *Mycobacterium tuberculosis* (Mtb), *Burkholderia mallei* and *Burkholderia pseudomallei*. Slated for this year are investigations using Mtb + SIV, in addition to continuations of some of the above-mentioned studies. Animal models used thus far include rhesus macaques, cynomologus macaques, rabbits and mice.

De la Garza shares other clinical and research responsibilities throughout the Institute. She is routinely called upon to provide clinical support for the chimpanzee colony. Chimpanzees exhibit disease states that closely mirror those of humans. As such, they provide an invaluable model for human disease. Owing to their obvious similarity to humans, they may develop many of these same conditions through the natural progression of life, thus requiring thorough clinical monitoring. SNPRC's animals are provided the care they need through the expertise of veterinary staff as well as by interacting with colleagues in human medicine. Other areas where support is provided by de la Garza include the ABSL-4 facility as well as the various animal colonies as required.

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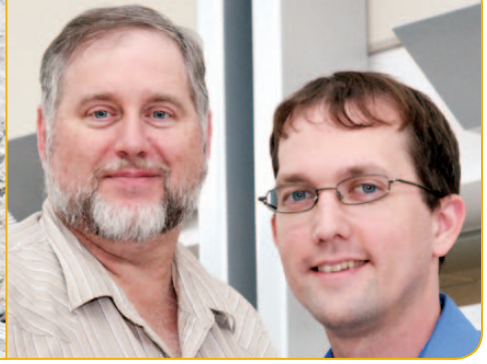
Staff

Left to right: David Vandenberg, Laura Rumpf, George Villanueva, Melissa de la Garza, Kathleen Brasky, Alberto Torres, Matthew Stautzenberger



"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 center's nonhuman primate resources, educate interested individuals, and to assist intramural and extramural investigators in designing and conducting research with these animals.

Our 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 the Biomaterials Services to ensure processing and storage of unique and special pathological tissues.
- Educating interested individuals in pathology and laboratory animal medicine.
- Pursuing collaborative research efforts and publishing results in the scientific literature.

Publications

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Staff

Left to right: Rosie Cordova, Jacob Martinez, Rita Sholund, Edward Dick Jr., Michael Owston, Cathy Snider, Michaelle Hohmann, Jesse Martinez, Maureen Robbins

"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."

Thomas M. Folks, Ph.D.

Associate Director for Research Resources

In 2011, the Research Resources Division at the SNPRC sponsored more than 70 scientists with $28 million in government and private support from around the country in their nonhuman primate (NHP) research endeavors. Investigator-sponsored work has ranged from development of the marmoset as a model for Ebola and Marburg diseases, the effects of fetal nutrient restriction, the efficacy of TLR7 agonist for hepatitis B, and the use of ultrasonic microbubbles to reverse diabetes.

Folks works with two senior scientists who provide guidance and leadership in helping coordinate the division, Jera Pecotte, Ph.D., and Karen Rice, Ph.D. As the leader of the Biomaterials Services Group, Pecotte collects and distributes tissues for investigators worldwide; she also heads our Training and Outreach Programs. In 2010-2011, the Biomaterials Group distributed more than 1,000 NHP tissue, blood, or DNA samples to scientists for their ongoing investigations. Rice leads the Research Coordination Group, which receives, processes, and coordinates research requests by principal investigators who seek to use our NHP resources. These scientists who access the SNPRC to carry out their work are appointed as affiliates or adjunct scientists. More than 100 requests are made each year to utilize our NHP research resource.

The SNPRC has over 2,900 NHPs consisting of baboons, chimpanzees, macaques, and marmosets. Research Resources provides support to national and international scientists in gaining access to these animals. By utilizing our internal scientific expertise, research leaders specializing in particular biomedical areas — development and aging, chronic disease, infectious disease and biodefense, genetics, and translational medicine — provide guidance to external investigators seeking information on how best to use NHPs to model their study. Using this approach, the group has been able to optimize our resources and match the team of scientists with a veterinarian to accomplish the investigator's goals. The result has been a steady increase in the number of investigators who have come, as well as those who have 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=134**

Publications

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Staff

Left to right: Karen Rice, Thomas M. Folks, Jerra Pecotte

"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 who 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, M.S., D.V.M.
Bob Baker, D.V.M.

Close involvement in protocol development from inception to performance with investigators provides the division with the ability to support the project and offer this expertise to future programs. 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. A multitude of programs investigating the neonate have been supported, allowing them to develop infectious disease protocols in the neonate.

The metabolic group has an extensive program which includes the development of obesity model in the baboon, metabolic profiling, a surgical model of diabetes and longitudinal investigation of genetic, dietary influences on the cardiovascular system, and influences 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 prosthetic devices. Multiple surgical suites with the ability to monitor, diagnose and meet the unique needs of these surgical patients and the ability to provide intense post-operative care to the patient is crucial. 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 division's ability to perform pharmacokinetic and vaccine development studies is long standing.

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Staff

Left to right: Gabriel Hernandez, Verla Atkins, Lauren Brown, Patrice Frost, Travis Church, Bob Baker, Abel Moncivais, Cassondra Bauer, Joe Jimenez Jr., Sharon Price, Michael Garcia

"The main goal of the Behavioral Services Program is to provide animals an environment that encourages the expression of species-typical behaviors, such as social interaction, locomotion, manipulation, and feeding, in a captive setting."

Corrine Lutz, Ph.D.

Leader, Behavioral Services, SNPRC

The Behavioral Services program uses accumulated knowledge of the natural history and behavior of each species housed at SNPRC to develop appropriate behavioral management and enrichment plans and to promote animal welfare. The program objectives include providing proper socialization and environmental enrichment, utilizing positive reinforcement training, monitoring animal behavior and providing interventions when necessary, educating the staff, and providing research support.

Providing social contact is the best way to encourage natural behaviors of nonhuman primates. 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. 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.

Environmental enrichment also includes structural, food, sensory, and manipulable enrichment. All enclosures are equipped with some form of structural enrichment such as climbing structures, perches, or swings. Baboons, chimpanzees, and other monkeys are quite agile and like to rest in areas above the ground. In addition to the standard nutritional diet, the primates are provided with food enrichment in the form of a variety of fruits and vegetables. Additional treats may include yogurt, popcorn, or raisins. Some foods are placed in foraging devices or puzzles to create added challenges. A sensory enrichment component includes music, nature videos and children's programming on television, and mirrors so animals can view themselves or their neighbors. The animals also receive a wide variety of toys and other objects to manipulate. Toys are rotated and replaced to keep the animals' interest.

In addition to enrichment, the behavioral team provides a range of services to support both colony management and research. An animal trainer works with care staff and technicians to train animals for routine husbandry and clinical procedures such as shifting cages and presenting body parts for inspection or injection. Training provides positive human interaction, reduces stress on animals, and makes staff responsibilities easier. The Behavioral Services staff conducts routine observations on many of the animals to assess their well-being. In situations in which the animals may need extra attention, a behavioral intervention plan is instituted. Interventions may include additional or different enrichment or movement to a new social group. Assessments and interventions help us to provide individuals with optimal housing and social settings.

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. To further educate the staff, Behavioral Services teaches classes that cover the natural history and behavior of nonhuman primates, animal training, and environmental enrichment.

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

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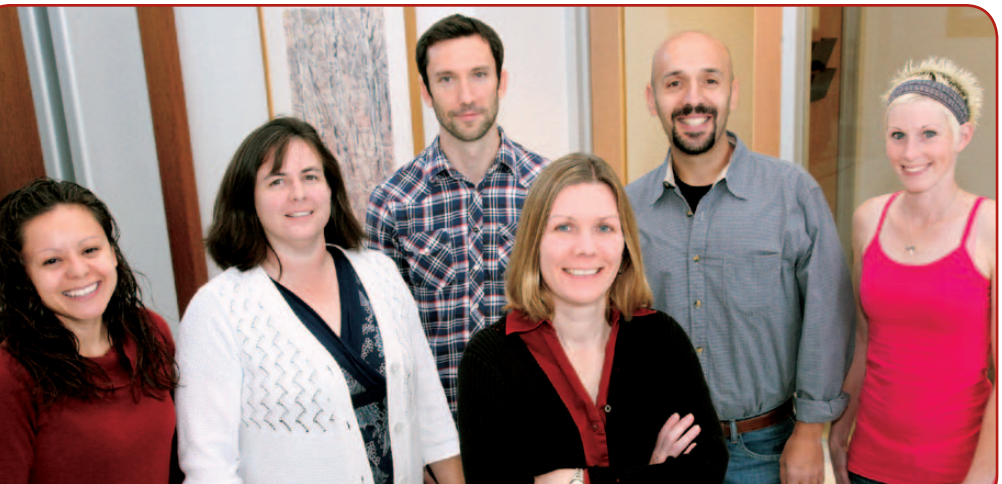
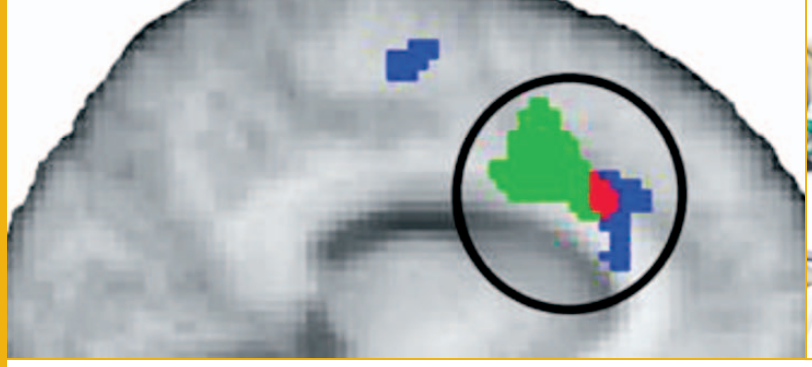


Staff

Left to right: Maribel Vazquez, Kim Linsenbardt, Blake Harrington, Corrine Lutz, Heath Nevill, Sabrina Bourgeois



"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 Shade, Ph.D.

Associate Scientific Officer

The research team received a renewal of a major 3-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, Princeton University and the University of Melbourne in Australia. The major objective of this research program is to define the neural mechanisms that contribute 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 initiated a new 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 will accomplish this comparison using anesthetized baboons for the study subjects. The protocol development has shown that some baboons are extremely tolerant of LBNP and some are not tolerant. 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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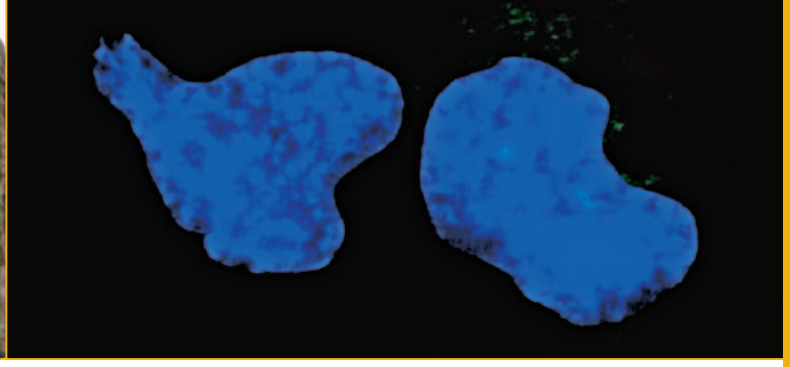
Staff

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, which are fed several different challenge diets in order to detect genetic and environmental influences on risk of cardiovascular disease. In both species, they have identified genes that affect levels of good cholesterol (LDL) or bad cholesterol (HDL) in the blood when the animals are fed a high-cholesterol diet. They also have demonstrated in baboons that 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. In another project with laboratory opossums, they are investigating how gene expression patterns change in spinal cords as newborn animals lose the remarkable ability that they have at birth to repair severed spinal cords. In addition, they have recently established that opossums can serve as hosts to implanted human cancer tissue, paving the way for research on genetic mechanisms, as well as drugs and other environmental factors that exert control over the growth and metastasis of various forms of human cancers.

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 they dissect the genetic and environmental factors that contribute to physiological processes in healthy and disease states, the team will be able to translate the knowledge gained to developing new preventions and treatments for human diseases. They are currently developing embryonic 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

Left to right, first row: Heather Ramirez, Martin Carias, Ernest Morin, Jane VandeBerg, Cristina Leandro. Second row: Janice MacRossin, Don Taylor, John VandeBerg, Qiang Shi, Mari Hui, Jeannie Chan, Susan Mahaney, Chéri Spencer. Third row: Sam Galindo, Allen Ford, Marcelo Leandro.
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Design and Production: Jeffrey Heinke Design

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