2004 Report of Progress

Southwest Foundation for Biomedical Research

"It has always been my intention to work toward the building up of a greater center for human progress through scientific research."

— Tom Slick Jr.
Founder
Southwest Foundation for Biomedical Research

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CREDITS

The 2004 Report of Progress is a publication of the Southwest Foundation for Biomedical Research.

Editor/ *Julie Collins, director of communications*

Design and production/ *Jeffrey Heinke Design*

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SFBR

SFBR
Southwest Foundation
for Biomedical Research

LETTER FROM THE PRESIDENT

Anthony J. Infante, M.D., Ph.D

As the new president of Southwest Foundation for Biomedical Research, I am pleased to present this report of progress for the year 2004.

Under the excellent leadership of recently retired President Frank F. Ledford Jr., M.D., SFBR has undergone remarkable growth and maturation during the past 13 years. My job is made all the more exciting by the opportunity to build on this great legacy.

Ultimately, all of us at SFBR are working to advance the dream of our organization's founder, Tom Slick, who envisioned a "city of science" in South Texas for "advancing human health through scientific discovery." Well ahead of his time for San Antonio in 1941, his vision is still relevant today. Mr. Slick also clearly articulated the issue of scientific impact when he suggested that SFBR should grow as big as it could without sacrificing scientific excellence.

Where are we today with respect to this grand vision? Through the efforts of our scientists and support staff, we can be proud of our strong rankings among organizations that receive funding from the National Institutes of Health, both overall and with respect to our peers in the Association of Independent Research Institutions (AIRI). In addition, many of our scientists enjoy well-deserved national reputations as experts in their fields, and their publications regularly appear in first-rate journals.

SFBR is a leader in addressing regional, national and even international health concerns. We have strong research programs in specific diseases and conditions of particular concern to the South Texas population, such as diabetes, obesity, and emerging infectious diseases; innovative programs in tropical diseases; long-standing research on diseases of global impact, such as cardiovascular disease, AIDS, and hepatitis; and a burgeoning program aimed at defeating infectious agents viewed as potential bio-terror threats. Truly, SFBR is a vital part of our city's thriving bioscience industry, San Antonio's newest "winning team."

SFBR has assembled a unique toolkit for our current scientists

as well as potential recruits. These include the SBC Genomics Computing Center, the Southwest National Primate Research Center, including our pedigreed baboons and other primate colonies, and a constellation of state-of-the-art bio-containment laboratories for bench and animal research that may be unique in the United States.

Certainly, SFBR has made great strides since its founding in 1941, with a period of unprecedented growth and accomplishment over the past decade. Our employees are proud to participate in the life-saving efforts of one of the leading independent biomedical research institutions in the United States.

As I begin my tenure as president, I am committed to taking SFBR to an even higher level of achievement. My vision for SFBR includes the following components:

- A stronger national and international reputation for discovery research in important areas of global human health. This reputation will be based on the successes of our individual scientists and their research teams, as well as our institutional reputation.
- Enough intellectual "critical mass" to tackle important problems in a meaningful way, either alone or in collaboration with local or remotely located associates.
- A focused five-year scientific plan that will map out aggressive and nimble strategies for acquiring research grants and contracts, retaining key scientists, and recruiting the best new scientific talent available.
- Continued efforts to provide a modern, attractive and efficient campus that will enhance the efforts of our scientists and assist in recruiting new faculty.
- An endowment proportional in size to the best U.S. research universities and private research institutes. In order to accomplish this we will inform, involve and inspire our potential philanthropic donors.

We will be moving forward with implementation of this vision in the coming months, during which time every facet of our operation will be examined and optimized. With a strong foundation already in place – a foundation laid by the hard work of our dedicated Board of Directors, creative and productive scientists, and hard-working staff – I believe SFBR is assured of a bright future. I look forward to reporting on the development of our strategic vision and further scientific progress in the near future.

Anthony J. Infante, M.D., Ph.D
President

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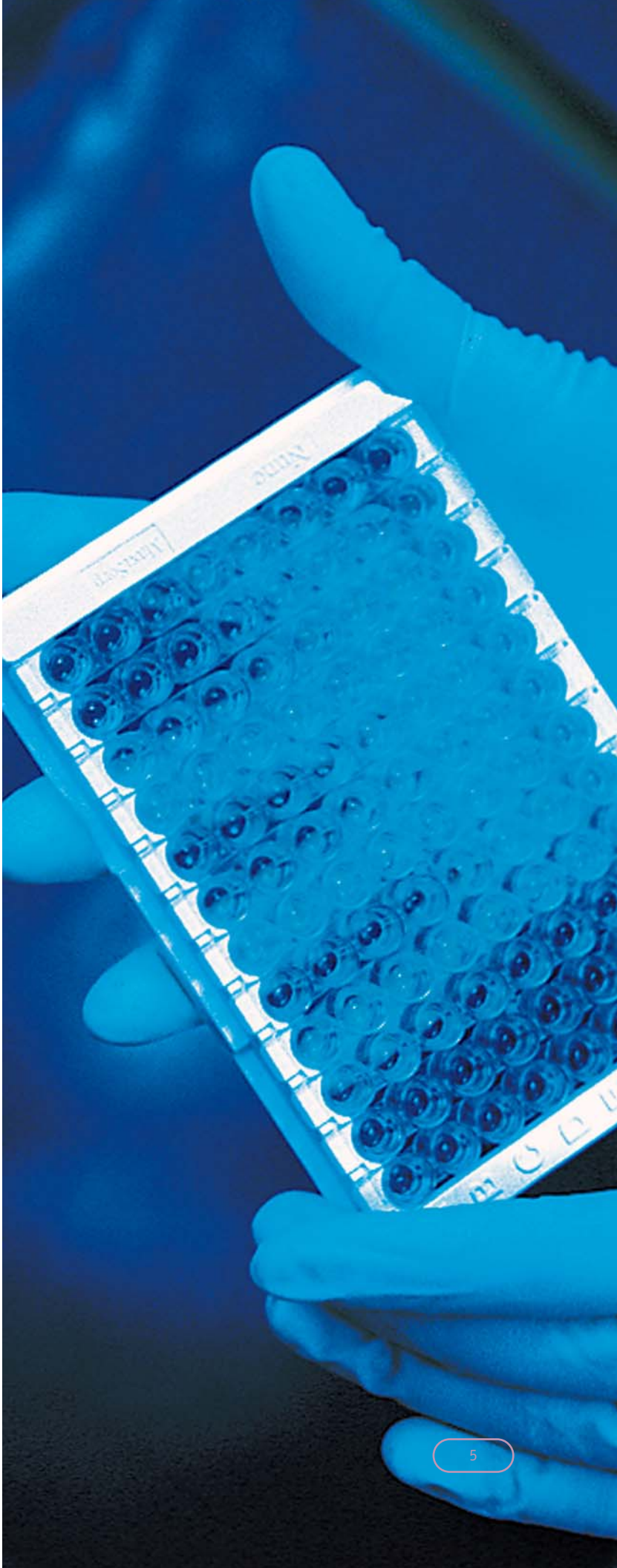

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IN MEMORIAM

Vaughan B. Meyer

December 13, 1920 – May 26, 2005

Vaughn B. Meyer, who lent his wisdom and leadership to SFBR and its governing board for more than 45 years, passed away on May 26, 2005, at the age of 84.

Mr. Meyer was appointed to the Foundation's Board of Governors in 1959, and from that point on, he gifted the organization with immeasurable time and effort as he worked to advance the vision of SFBR founder Tom Slick. His distinguished service included a term as chairman from 1960-1961, as well as other roles over the years on the board's executive and finance committees. Designated as trustee emeritus in 1999, he remained active on the board until his death.

Mr. Meyer also served SFBR through his leadership role with The Argyle. His 45 years on the club's governing board began in 1954 and included five terms as president. As a unique private club dedicated to the support of SFBR, The Argyle is an important partner in the Foundation's success, and Mr. Meyer applied his vision and enthusiasm to helping both organizations achieve their full potential. The Argyle Verandah is named in his honor as a tribute to his outstanding contributions.

In addition to his support of Southwest Foundation for Biomedical Research, this hard-working family man dedicated himself to many worthy causes during his lifetime. After his distinguished service to the U.S. Navy as a mechanical engineer during World War II, he became a successful owner and chief executive of several lumber, home construction and land development companies. What he earned and learned from his career he applied to contributions to and voluntary leadership roles with numerous community organizations working in the areas of education, health care, social service and community development.

He leaves behind him a legacy that endears him to the hearts of all those touched by his good works.

May Dougherty King

December 30, 1913 – August 9, 2004

Southwest Foundation for Biomedical Research lost a long-time friend and supporter on August 9, 2004, when May "Topsy" Dougherty King, trustee emeritus, passed away at the age of 90. A resident of Corpus Christi, Texas, Mrs. King was a world traveler, art collector, tireless volunteer, and philanthropist who made countless contributions to education, the arts, health care, and political causes, both on her own and as chairperson of the James R. Dougherty Jr. Foundation, funded by the estate of her father, James R. Dougherty Sr.

Mrs. King was a close friend of SFBR founder Tom Slick and supported his dream of building "a great center for human progress through scientific research." She served as a member of the Foundation's Board of Governors since 1966 and was designated trustee emeritus in 1990.

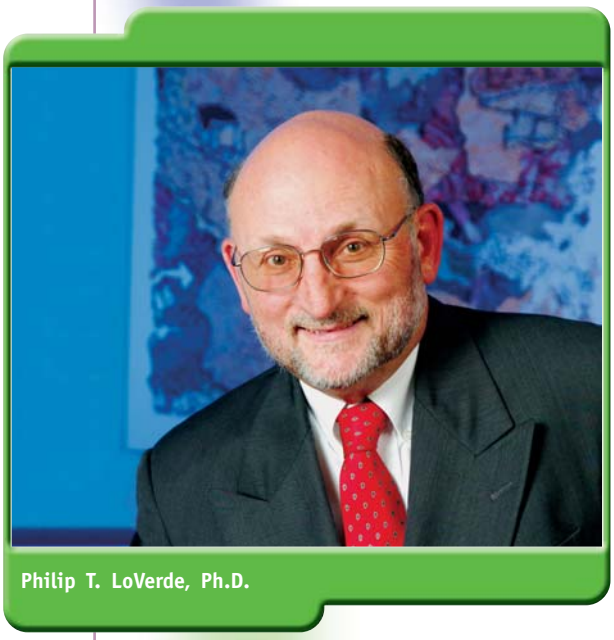
During her many years of leadership, friendship and support of the Foundation, she made numerous financial contributions to help SFBR advance its mission of improving human health. These include the funds to construct the James R. Dougherty Jr. Memorial Research Laboratory, which houses animals from the Foundation's colony of nonhuman primates that require specially controlled environmental conditions for their well-being. The facility also is home to the Foundation's valuable pedigreed colony of laboratory opossums, which serve as an important model for research on cancer, heart disease, the repair of spinal cord injury, and many other pressing matters of human health.

Through a gift from her estate, she also established the May Dougherty King Endowment at SFBR. This generous endowment will support the life-saving and life-improving research of the Foundation for years to come.

The faculty and staff of SFBR join the Board of Trustees in bidding their close friend a fond farewell.

SCIENTIFIC REPORTS

LETTER FROM THE SCIENTIFIC DIRECTOR



Philip T. LoVerde, Ph.D.

As I introduce the scientific progress achieved at SFBR during 2004, let me also introduce myself to the Foundation's many friends and partners.

In May 2005, I began serving full time as the Foundation's new scientific director after a long tenure at the State University of New York, where I served as distinguished professor in the Department of Microbiology and Immunology.

Actually, I have been integrating myself into the responsibilities of my new position since September 2004, when I began working at SFBR half-time while keeping my position half-time at SUNY. During this transition period, Dr. William Stone, a professor emeritus from Trinity University, lent his leadership to SFBR as its interim scientific director. As he dealt with the day-to-day issues of this position, he and I together made decisions that focused on maintaining and building upon the Foundation's reputation as one of the nation's leading independent biomedical research institutions. The Foundation owes a debt of gratitude to Dr. Stone, an outstanding teacher and administrator, and a true friend to SFBR.

This summer, work was completed on the Ledford Building, named in tribute to the Foundation's recently retired president, Dr. Frank F. Ledford Jr., and home to my new research laboratory. This allows me to relocate my own research program on schistosomiasis – a parasitic disease that afflicts more than 200 million people in 76 countries – as I whole-heartedly take on the position of scientific director.

This responsibility is exciting to me because of SFBR's world-class scientists and the exceptional staff who support them. Collectively and individually, SFBR scientists have made distinguished contributions to basic biomedical science. Basic science is the engine that drives discovery, and in each of our departments, that engine is roaring.

In the Department of Genetics, scientists lead innovative programs that are quickly advancing our knowledge of the genetic causes of cardiovascular disease, diabetes, obesity, osteoporosis, parasitic diseases, psychiatric disorders, and other complex diseases. Their monumental efforts are greatly accelerated by the unparalleled resource of the SBC Genomics Computing Center and the development of novel statistical methods that SFBR geneticists have made available to researchers worldwide.

The Department of Virology and Immunology studies some of the most

important viral diseases of our day, including HIV, hepatitis C, dengue, SARS and Ebola. Our virologists continue to make major contributions in the hunt for vaccines and treatments to eradicate these health threats. They are better able to do this important work because they have access to some of the best laboratories in the world, including the nation's only privately owned maximum-containment laboratory.

The Department of Physiology and Medicine continues its long-standing, internationally recognized research on cardiovascular disease while also gaining attention for its efforts in cancer drug discovery. Meanwhile, the Department of Organic Chemistry continues to make significant contributions to safer, more effective contraception methods and the treatment of reproductive disorders. Recognized as a premier research group for steroid synthesis, the department holds several patents in this area, including a new patent awarded in 2004.

Nonhuman primates are uniquely suited as animal models for many human disorders, and the ability to work with these animals has enabled many of the life-saving and life-improving advances achieved by SFBR scientists. It also has enabled innovative, collaborative biomedical research with scientists from other institutions around the country.

The Foundation's primate colonies – along with the valuable expertise of SFBR scientific and veterinary staff – have been growing in importance as a national resource since the National Institutes of Health established the Southwest National Primate Research Center at SFBR in 1999. In 2004 alone, the SNPRC provided resources and expertise to 144 investigators from 28 states and four foreign countries in an effort to advance research on common chronic diseases, developmental abnormalities, infectious diseases, and a wide variety of other health concerns.

SFBR's valuable research with animals would not be possible without the dedicated faculty and staff of the Department of Comparative Medicine, who provide outstanding care for the Foundation's animal colonies and skilled support for the vital research that relies on them.

Together, SFBR scientists had a highly productive year in 2004, publishing nearly 120 papers in refereed journals highlighting their progress. They also competed successfully for a record-setting $58.4 million in new research grants and contracts. This amount includes a $27.9 million, five-year renewal of the SNPRC base grant from the NIH, the largest grant in SFBR history. While these achievements are measures of success, the real contributions of our scientists lie in their numerous discoveries for the benefit of human health.

As the new scientific director, one of my first orders of business is to work with our new president, Dr. Anthony Infante, and other scientific leadership to develop a strategic plan for SFBR's future. This plan will be based upon the established strengths and areas of excellence of our faculty, research and assets, and it should serve as a roadmap to focus and guide SFBR to achieve further scientific progress and prominence. I look forward to reporting to you on the progress of this strategic plan and how it will define SFBR in the future.

These are exciting times for SFBR. The following pages of this report highlight our successes in 2004, and I anticipate even greater things to come in 2005.

Philip T. LoVerde, Ph.D.
Scientific Director

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MAJOR SCIENTIFIC ACHIEVEMENTS

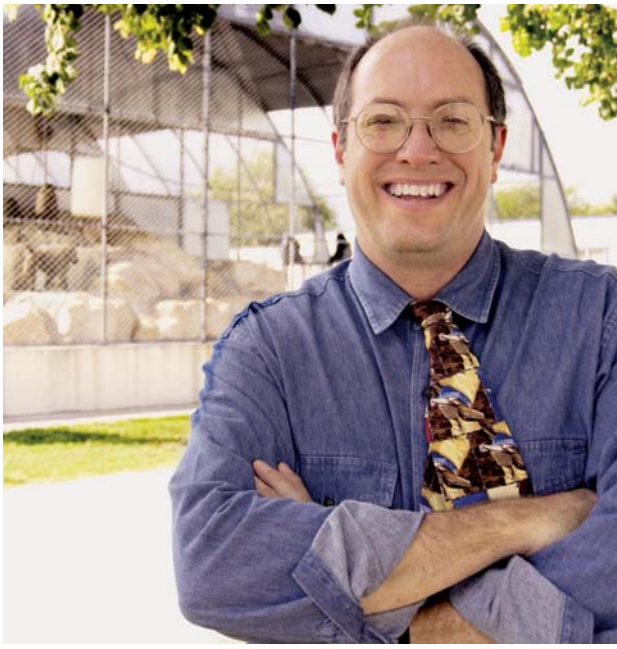
Highlights of progress in 2004

Scientists find genetic influences on heart disease, diabetes and obesity

As part of their world-famous research on the genetic determinants of common diseases, scientists in the Department of Genetics localized genes influencing a variety of traits related to cardiovascular disease, including genes that influence levels of HDL-cholesterol and LDL-cholesterol, as well as a person's heart rate.

Dr. John Blangero contributed to the identification of a recently cloned novel gene, BEACON, which influences traits related to the metabolic syndrome. The metabolic syndrome is a set of related diseases that include obesity, diabetes and heart disease, and it is recognized as a major public health problem in the United States, particularly in minority populations.

Dr. Tony Comuzzie directed a study that demonstrated for the first time that there are heritable components to gene expression in fat tissue. This work has opened new avenues for research focused on understanding tissue-specific traits related to heart disease and obesity.



New understanding of the growing resistance to anti-malarial drugs

Dr. Tim Anderson and Ms. Shalini Nair co-authored a major publication in the journal *Science* documenting how increased resistance to anti-malarial drugs has spread from Asia to Africa as drug-resistant parasites have "jumped continents" via international travelers. Through a collaborative study with researchers at the London School of

Hygiene and Tropical Medicine and other collaborators in Asia and Africa, the researchers showed that, contrary to common presumptions, genetic mutations that give malaria parasites their increased drug resistance are rare. When those mutations have occurred, the mutant parasites have been exported from one region or continent to another, resulting in a rapid spread of resistance to low-cost malaria treatments and a rise in malaria's death toll. Drug resistance is a serious problem in dealing with malaria, which kills more than a million people per year. Dr. Anderson's research has significant implications for approaches to help control malaria in Africa, where the disease kills a child every 30 seconds.

Development of novel statistical methods for finding disease-influencing genes

Dr. Jeff Williams developed new statistical methods for assessing genetic effects on discrete traits, which are either present or absent in an individual as opposed to being measurable in quantities or degrees, as is the case with quantitative traits such as weight, blood pressure, blood cholesterol and glucose levels. The ability to analyze discrete traits, such as seropositivity for infection with a parasitic organism – which indicates whether an individual is infected or not – has presented a serious challenge in genetic epidemiology in the past. However, this latest work by Dr. Williams has opened new opportunities for assessing the genetic components of susceptibility to traits that can only be assessed qualitatively.

Baboons help scientists find genetic influences on psychopathology

Dr. Jeff Rogers and his colleagues were able to assess the genetic determinants of monoamine metabolites related to severe psychiatric disorders using evaluations of cerebrospinal fluid in the baboon model. It would not have been possible to collect cerebrospinal fluid from many members of large human families, and the important findings of genetic effects associated with the risk of psychopathology would not have been discovered without the baboon model.

Discovery of a useful tool for developing novel therapies for hepatitis B

Dr. Robert Lanford and his research team have identified a sequence in the hepatitis B virus (HBV) envelope protein responsible for interaction with the cellular receptor. Synthetic peptides based on this sequence block the infection of liver cells with hepatitis D virus (HDV). Since HBV and HDV use the same envelope and cellular receptor, researchers often use HDV as a surrogate model for HBV in receptor studies. Dr. Lanford's group found that the minimum sequence to block infection was a 15 amino acid peptide. This peptide will be a useful tool in the search for the unknown receptor and could be used to develop novel antiviral therapies that block HBV infection.

Strides in fighting the "silent epidemic," hepatitis C

Hepatitis C is often called the silent epidemic because individuals can harbor the virus for years without awareness of infection until they start showing signs of liver disease.

Chimpanzees provide an invaluable model for research on potential vaccines and better therapies for hepatitis C because, other than humans, they are the only animals susceptible to infection. Some chimpanzees are able to clear their infection, and others that remain chronically infected typically never progress to liver disease as humans do. Through his studies of hepatitis C in chimpanzees, Dr. Robert Lanford achieved two significant findings in 2004.

Dr. Lanford's laboratory performed an analysis of changes in gene expression in the liver of chimpanzees infected with the hepatitis C virus (HCV). Using microarray technology that examines 22,000 genes simultaneously, he found alterations in 162 genes during chronic infection. Many of these genes represent interferon response genes, providing the first insight to innate immune factors that may limit the amount of viral replication in the liver and thus protect individuals from rapid liver destruction.

Another finding of Dr. Lanford gained national attention when he published study

results in the *Journal of Virology* showing that chimpanzees that have previously cleared infection with one genotype, or strain, of HCV are protected from re-infection with a different, highly divergent strain of the virus. This is the first evidence of cross-genotype protective immunity to HCV, and it suggests that it should be feasible to produce a vaccine that will be protective against all strains of the virus.

Immune interactions: The relationship among HIV, hepatitis C, and rapid progression to liver disease

A paper co-authored by Dr. Krishna Murthy in *Science* in 2004 showed the critical role two types of white blood cells play in a person's or chimpanzee's ability to clear infection with hepatitis C. It also shed light on why the many individuals who are co-infected with HIV and the hepatitis C virus (HCV) suffer from a rapid progression to liver disease. While many chimpanzees that have previously cleared infection with HCV can quickly clear a new infection with the virus, a study by Dr. Murthy's research group revealed that chimpanzees with depleted CD4+ T cells could not clear a second infection. The response of CD8+ T cells alone was insufficient. This indicates that both CD4+ and CD8+ T cells are needed to control HCV infection, and that when the function of one is lost or inhibited, the disease progresses more rapidly. This is especially significant to people who are co-infected with HIV and hepatitis C, since HIV causes a depletion of CD4+ cells. Other investigators have reported that in patients with co-infection, liver disease is more severe and progresses rapidly when compared to patients with only HCV infection.

Specific gene found to play an important role in susceptibility to HIV infection and progression to AIDS

A collaborative study that involved researchers from the University of Texas Health Science Center at San Antonio, several other local and national institutions, and Dr. Krishna

Murthy at SFBR revealed a correlation between people's genetic susceptibility to HIV and AIDS and the number of copies they carry of a gene that codes for a protein known as the CCL31 chemokine. Study results published in *Science* showed that individuals carrying a lower number of copies of the gene showed increased susceptibility to HIV infection and subsequent progression to AIDS. On the other hand, people with a higher number of copies of the gene showed increased resistance to HIV infection and, if they did become infected, slower progression to AIDS. Interestingly, chimpanzees have even higher copy numbers of the gene and do not progress to AIDS when infected with HIV.

New compound shows promise as potential cancer drug

In a collaboration with Dr. Paul Wender at Stanford University, Dr. Susan Mooberry's laboratory tested synthetic derivatives of laulimalide, a natural compound extracted from a tropical Pacific sponge that has previously been shown to work in a manner similar to a current cancer drug called Taxol. Laulimalide shows efficacy against some Taxol-resistant cells, but it is prone to chemical breakdown and can thereby lose its activity. Dr. Mooberry's tests found that two synthetic derivatives designed and synthesized by Dr. Wender to maintain their chemical stability show the same promising biological activities of laulimalide, meaning they stabilize cellular microtubules, which interrupts normal cell division and thus causes cancer cells to self-destruct by turning on a cellular suicide program. The two research groups published these promising findings in the highly prestigious *Proceedings of the National Academy of Sciences of the United States of America* in June 2004. Recently, the journal recognized the article as one of its 100 most cited articles for the year.

Patent awarded, trials begin related to antiprogestin developed at SFBR

The potential applications of selective progesterone receptor modulators involve contraception as well as the treatment of endometriosis, progesterone-dependent tumors, uterine fibroids, premenstrual syndrome and adverse symptoms of menopause. The antiprogestin known as CDB-4124 was conceived and synthesized by the laboratories of Dr. P.N. Rao, and subsequent biological testing indicated that the analog exhibits three times the antiprogestational activity of its parent compound with significantly decreased side effects. While patents are pending for this compound and several derivatives, in July 2004, the United States Patent and Trademark Office issued U.S. Patent Number 6,768,014, which covers Dr. Rao's improved methods for synthesizing CDB-4124.

Under the trade name Progenta™, CDB-4124 has been licensed to Zonagen Inc. for development in the treatment of uterine fibroids, endometriosis and progesterone-dependent breast tumors. In June 2004, Zonagen Inc. initiated a European Phase I/II study of Progenta™ to assess its safety and efficacy for the treatment of uterine fibroids. Preliminary results released by Zonagen Inc. in September and November 2004 indicate that Progenta™ is well tolerated with no negative side effects and achieved statistically significant reduction in fibroid size compared to a control group. Progenta™ also performed favorably when compared to a positive control group using Lucrin®, a GnRH agonist commonly administered for the treatment of fibroids.

DEPARTMENT OF GENETICS

During 2004, the Department of Genetics made dramatic progress in addressing its mission to advance human health through genetic research.

Working with both animal and human populations, departmental scientists made major contributions towards advancing our knowledge of the genetic determinants of cardiovascular disease, diabetes, obesity, hypertension, stroke and parasitic diseases. They also improved the tools available for genetic research through development of innovative statistical methods and refinement of unique animal models for human disease. To support these important research efforts, departmental scientists generated over $15.8 million in grant funding during 2004.

Advances in the genetics of cardiovascular disease and metabolic syndrome

Cardiovascular disease has traditionally been the primary focus of research in the Department of Genetics, and the department maintained this focus during 2004 with $6.7 million in grant funding awarded to support genetic studies of heart disease. Departmental researchers took full advantage of the power of the SBC Genomics Computing Center as they conducted genome scans for heart disease-related traits in seven different human populations and SFBR's unique pedigreed baboon colony. These studies localized genes influencing HDL-cholesterol (the "good cholesterol"), LDL-cholesterol (the "bad cholesterol"), and heart rate.

Gene localization is the first step toward identification of the genes responsible for disease, and departmental scientists have continued to make major advances in the development of statistical techniques for helping scientists move from their knowledge of the area of the human genome that contains a disease-influencing gene to knowing which specific gene is responsible for the trait variation.

Using the unique combination of expertises available in the Department of Genetics and the power of the SBC Genomics Computing Center, Dr. John Blangero contributed to the identification of a recently cloned novel gene, BEACON, which influences traits related to the metabolic syndrome. The metabolic syndrome is a set of related diseases including obesity, diabetes and heart disease, and it is recognized as a major public health problem in the United States, particularly in

minority populations. Knowledge of the genes that influence this important cluster of diseases will facilitate the development of new mechanisms for prevention and treatment of the disorder.

In addition to focusing on characteristics traditionally associated with heart disease, departmental scientists have pioneered the use of levels of gene expression in specific tissues as novel phenotypes to provide new insights into the genetic basis of cardiovascular disease. In a study directed by Dr. Tony Comuzzie, departmental scientists demonstrated for the first time that there are heritable components to gene expression in fat tissue, thereby opening new avenues for research focused on understanding tissue-specific traits related to heart disease.

Developing new animal models to advance understanding of various diseases

Animal model development was the second most highly funded area of departmental research during 2004, with a total of $2.9 million in funding awarded. Much of this research was supported by the Southwest National Primate Research Center, which fosters the development of nonhuman-primate models for human disease. Work conducted in the department as part of the primate center's efforts is focused on developing the baboon as a model for diabetes, obesity, Chagas disease and neuroimaging research. A new initiative supported by an independent grant from the National Center for Research Resources to Dr. John VandeBerg is focused on developing a rhesus monkey colony in Nepal to address the critical shortage of these animals for research, particularly in the area of AIDS-vaccine development.

As the nonhuman primate with by far the highest susceptibility to epilepsy and seizures, the baboon is uniquely suited as a model for studying the genetics of photosensitive epilepsy, a condition that is frequently inherited but difficult to study in humans. In addition, the baboon colony at SFBR provides scientists with an especially valuable resource for finding the genes that influence susceptibility to this and a host of other disorders. Family relationships among the animals in the pedigreed baboon colony have been carefully documented for many years, and a genome scan has already been performed on the colony as part of the department's ongoing research on heart disease. This means that each individual animal has been characterized for approximately 400 genetic markers, allowing scientists to examine how those specific markers are associated with disease.

In 2004, Dr. Jeff Williams was awarded a grant from the National Institute for Neurological Disorders and Stroke to take advantage of these unique features of the

baboon and the pedigreed colony by developing a baboon model for genetic research on epilepsy. Dr. Williams is seeking to identify the genes that influence variation in susceptibility to this disorder, which affects about 1 percent of the U.S. population. Knowledge of these genes could then be applied to help improve the diagnosis and treatment of epilepsy in humans.

The South American marsupial *Monodelphis domestica* was developed at the Southwest Foundation for Biomedical Research as an animal model for a broad range of diseases. The department's colony of these unique animal models received a generous grant from the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation for its support during 2004. The laboratory opossums historically have been used primarily in cancer research. In an expansion of the use of this model, a five-year grant from the National Institute for Diabetes and Disorders of the Kidney was awarded to Dr. John VandeBerg to support research on cholesterol-responsiveness genes in the *Monodelphis* as a model for heart disease.

Investigating varied susceptibility to infectious diseases

With a total of $2.4 million in grant funding awarded in 2004, the third most highly funded area of research in the department concerned the genetic determinants of variation in susceptibility to infectious diseases. Utilizing studies of large, extended families living in areas with high rates of parasitic disease, departmental scientists have demonstrated that there are significant genetic components to susceptibility to infection with parasitic organisms and to immunological traits associated with infection. One of these studies involves 1,500 members of large, extended families living in an area of rural Brazil with high rates of infection with *Trypanosoma cruzi*. The *T. cruzi* parasite causes Chagas disease, which is the leading cause of heart disease in Latin America.

Another major infectious-disease study is based in Nepal and focuses on the genetic determinants of susceptibility to intestinal worm infections. This study involves over 2,500 members of a single family, all of whom are involved in an ongoing genome scan. This large, well-characterized pedigree is extremely powerful for genetic research.

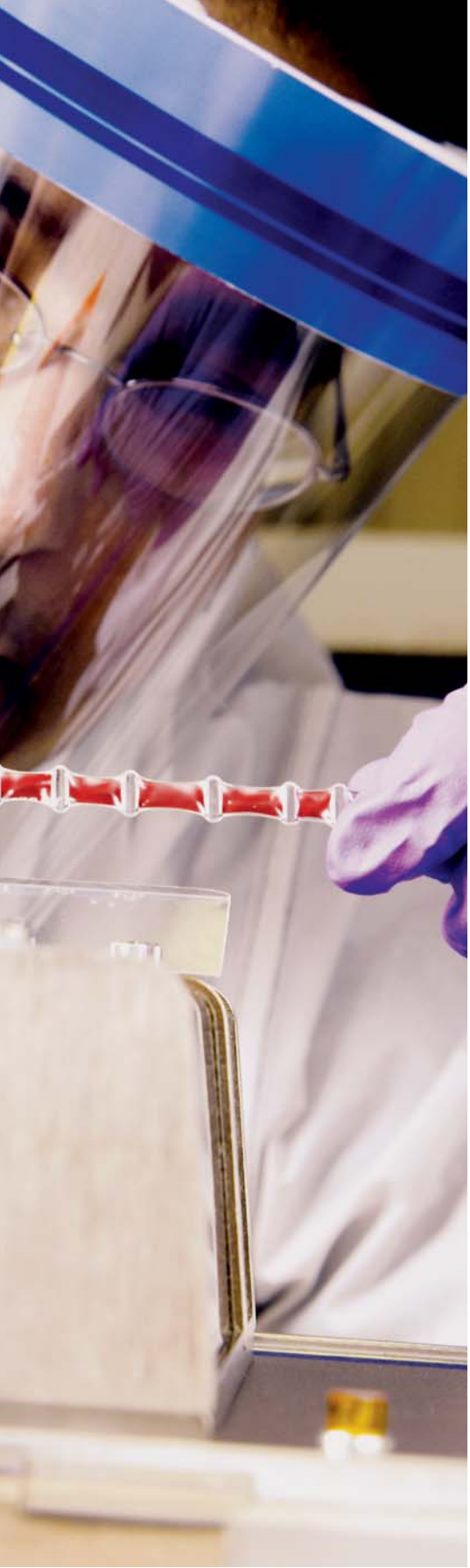
In addition to consideration of people's genetic variation in their susceptibility to infection, departmental scientists are also examining the genetic variation in the parasitic organisms themselves as part of efforts to improve treatment efficacy. For example, support from the National Institute for Allergy and Infectious Diseases is allowing Dr. Tim Anderson to explore the genetic determinants of drug resistance in malaria parasites. These parasites' increasing drug resistance is a tremendous prob-

lem in the treatment of malaria, a disease that is responsible for a million deaths per year worldwide.

In 2004, Dr. Anderson and his collaborators published a paper in the prestigious journal *Science* presenting research results that offer scientists a new understanding of how increased resistance to antimalarial treatments has spread from Asia to Africa as drug-resistant parasites have "jumped continents." This research by Dr. Anderson and his assistant Shalini Nair – conducted in collaboration with the London School of Hygiene and Tropical Medicine, the Medical Research Council of South Africa, and the Shoklo Malaria Research Unit of Thailand – has significant implications for approaches for controlling the spread of drug-resistant malaria in Africa, where the disease kills a child every 30 seconds.

Developing novel methods for finding disease-influencing genes

Development of new statistical methods for genetic analysis continues to be a major area of research in the Department of Genetics. With a total of $1.3 million in grant funding awarded to support these efforts, the department is an international leader in the creation of novel methods for determining the effects of individual genes on disease-related traits. Dr. Jeff Williams made a major methodological advance in 2004 with the development of new statistical methods for assessing genetic effects on discrete traits, which are physical characteristics that are either present or absent in an individual, as opposed to traits that are present in varying, measurable quantities or degrees. For example, quantitative traits that affect human health and disease – such as a person's weight, blood-cholesterol level, blood-pressure level, and glucose level – are found in every individual with measurable differences. On the other hand, with some disease conditions, an individual can only be described as "affected" or "unaffected." Such is the case with many psychiatric disorders such as schizophrenia, as well as with some infectious diseases. The ability to handle discrete traits such as seropositivity for infection with a parasitic organism – which indicates whether an individual is infected or uninfected – has presented a serious challenge in genetic epidemiology in the past. However, this latest work of Dr. Williams has opened new opportunities for assessing the genetic components of susceptibility to traits that can only be assessed qualitatively.



Searching for genetic influences on psychiatric disease

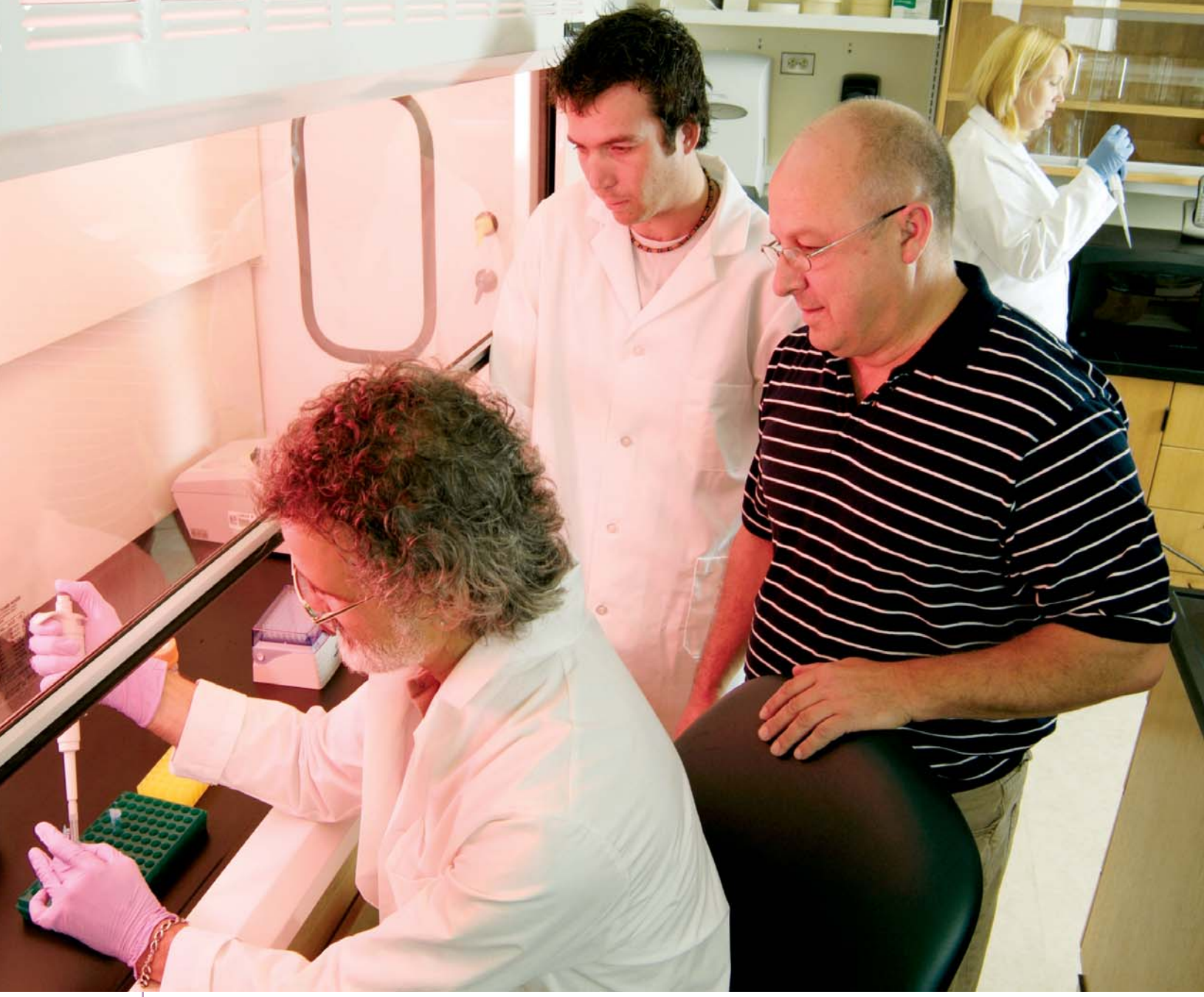
The department has a growing focus on the genetic determinants of psychiatric disease. This research area was supported by $1.1 million in funding during 2004. As part of a collaboration with investigators at Harvard University, Dr. Sarah Williams-Blangero was awarded a subcontract for assessing the genetic determinants of traits related to psychiatric disease in the pedigree of a large, extended family in Nepal that has been the subject of the department's research on helminthic infections. In another collaborative effort, Dr. Laura Almasy was awarded a subcontract to continue her research on the genetic components of alcoholism in humans.

As with many research programs in the department, research on psychiatric diseases in human populations is paralleled by research in a nonhuman primate model. The baboon model offers practical advantages for assessing physiological traits related to psychiatric disease that cannot be easily assessed in humans. For example, Dr. Jeff Rogers and his colleagues were able to assess the genetic determinants of monoamine metabolites related to severe psychiatric disorders as determined from cerebrospinal fluid in the baboon model. It would not have been possible to collect cerebrospinal fluid from many members of large human families, and the important findings of genetic effects associated with risk of psychopathology would not have been discovered without the baboon model.

Increasing focus on diabetes

Research on diabetes is an area of increasing focus within the department, with a total of $833,000 in grant funding. These efforts are led by Dr. Ravi Duggirala, who received two new grants from the National Institute for Diabetes and Disorders of the Kidney to support his research program on the genetic determinants of susceptibility to type II diabetes.

Dr. Jean MacCluer also received a major grant from the National Institute of Diabetes and Disorders of the Kidney in 2004 as part of a collaboration with the University of New Mexico. This project is examining the genetics of kidney disease in Zuni Indians, with the goal of identifying the individual genes influencing susceptibility to kidney disease in American Indian populations. American Indians are highly susceptible to kidney disease, which is commonly associated with diabetes, and the Zunis in particular are even more susceptible than other American Indians. Dr. MacCluer and her collaborators at the University of New



Mexico are working with this population to find genes that influence both diabetic and non-diabetic kidney disease in an attempt to develop new preventions and treatments for kidney disease in the broader population.

Increasing contributions to the scientific literature

The research achievements of departmental scientists in the areas listed above and in a variety of other projects were documented in 81 publications in the scientific literature in 2004. This record level of publication output indicates that the department is maintaining its strong momentum and will continue to make major contributions to the advancement of genetic research for the benefit of human health.

Scientific recruitment brings new research to SFBR

During 2004, it became apparent that the continued development of the exciting research programs ongoing in the department would require additional expertise in molecular genetics. As a result, the department sought to recruit an outstanding molecular geneticist who would be interested in participating in the department's internationally recognized research efforts in cardiovascular disease. This search was successful, with Dr. Eric Moses from the Royal Women's Hospital in Melbourne, Australia, joining the faculty early in 2005. His recruitment adds a new project on the genetics of preeclampsia to the research portfolio of the department.

Preeclampsia – toxemia during pregnancy characterized by the new onset of high blood pressure and other systemic dysfunction – is the most common serious disorder of human pregnancy and a major cause of preterm deliveries, yet little is known about its cause. Dr. Moses expects his close work with the department's renowned statistical genetics group to advance his search for genes that make women susceptible to this serious disorder. Resulting findings could provide physicians with more options for the prevention and treatment of preeclampsia and help them better manage women's pregnancies from the start.

Looking ahead

The significant advances made by the Department of Genetics in 2004 clearly indicate the potential for even greater scientific success in 2005 and beyond. This success will be supported by further improvements in the working space available to house the research programs of departmental scientists. Following the completion of the Ewing Halsell Wing and the Kleberg Wing of the molecular genetics building and the construction of the SBC Genomics Computing Center in 2003, planning is now underway to renovate the department's remaining old laboratories and offices during 2005. Clearly, it is an exciting time for genetics at the Southwest Foundation for Biomedical Research.

Doctoral Staff

(as of December 2004)

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David L. Rainwater, Ph.D.
Jeffrey A. Rogers, Ph.D.
John L. VandeBerg, Ph.D.

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Paul B. Samollow, Ph.D.
Jeff T. Williams, Ph.D.

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Laura A. Cox, Ph.D.
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Lorena Havill, Ph.D.
Jack W. Kent Jr., Ph.D.
Sandra L. Laston, Ph.D.
Dev R. Rai, M.B.B.S.
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Joohon Sung, Ph.D.
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Scientist Emeritus

William H. Stone, Ph.D.

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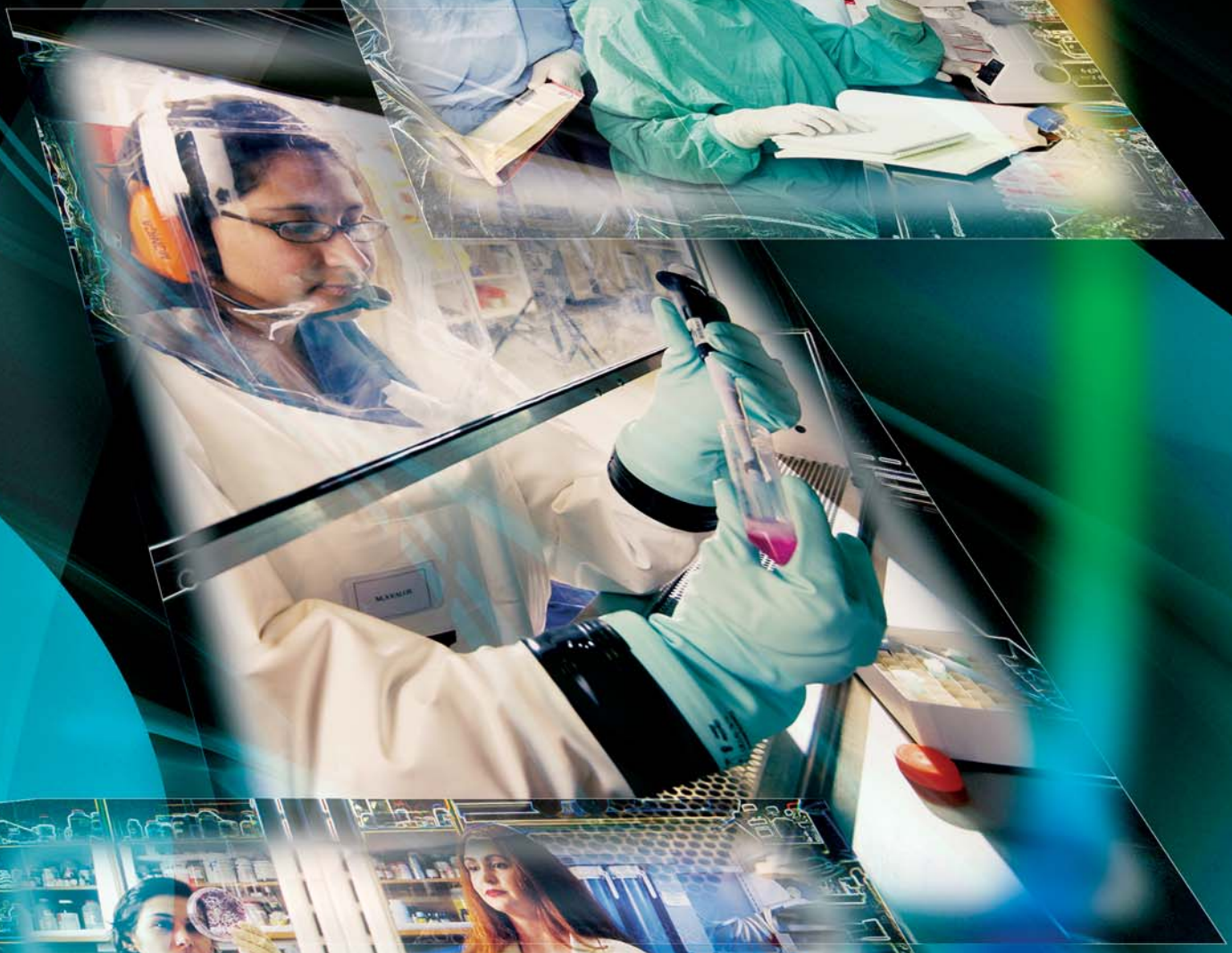
Sobha Puppala, Ph.D.
Cherise J. Rohr, Ph.D.
Qiang Shi, Ph.D.
M. Elizabeth Tejero, Ph.D.
Diane M. Warren, Ph.D.
Diedre A. Winnier, Ph.D

DEPARTMENT OF VIROLOGY AND IMMUNOLOGY



Scientists in the Department of Virology and Immunology understand the pressing nature of their research.

C H A I R

Jean L. Patterson, Ph.D.

HIV infects approximately 40 million people worldwide, and every 10 seconds, someone dies from AIDS. Approximately 200 million people worldwide are chronically infected with hepatitis C, dubbed the "silent epidemic" because people can carry the virus for years unaware of their infection – until they start showing symptoms of liver disease. Emerging and exotic viruses such as dengue have made their way across the U.S. border, while others such as Ebola, Marburg and SARS have wreaked havoc in other countries, with the potential for intercontinental spread. And as the war on terror presses on, biodefense initiatives focusing on anthrax, hemorrhagic fever viruses, and other select agents remain national priorities.

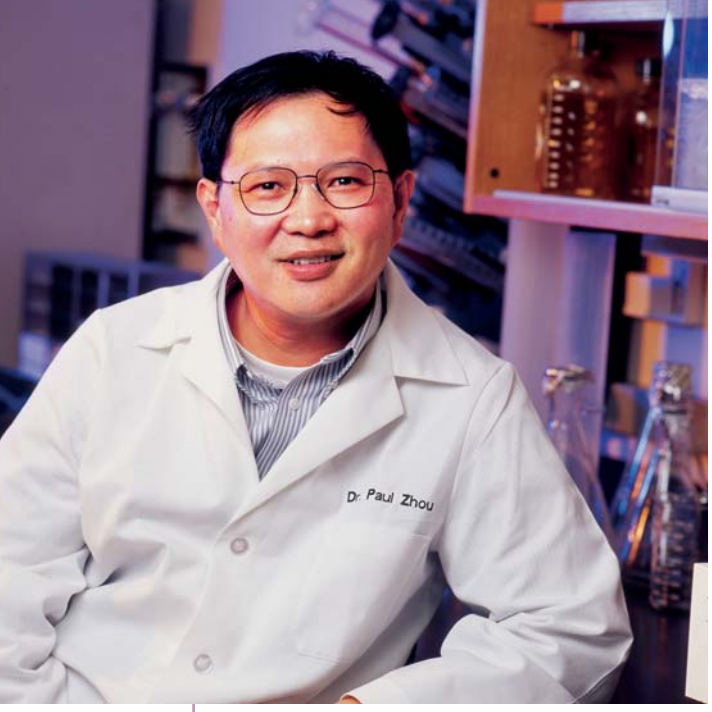
SFBR virologists are trying to devise strategies to defeat these and other maladies, and in their efforts, they have access to some of the best-equipped laboratories in the world, including the nation's only privately owned biosafety level four (BSL-4) laboratory. This space-suit lab is designed for maximum containment so that scientists can safely study deadly pathogens for which there are no treatments or vaccines.

Also extremely valuable to the department's efforts are the Foundation's nonhuman primates, which offer the most effective models for human infectious disease, as well as for the evaluation of therapeutic drugs and vaccines against viral agents.

AIDS

Despite advances in the treatment of HIV and AIDS, a vaccine has remained elusive, and new infections are on the rise. In the United States alone, the number of infected individuals jumped from 950,000 in 2003 to 1 million in 2004. As part of the national battle against this deadly virus, SFBR scientists are taking several different approaches to find its Achilles' heel.

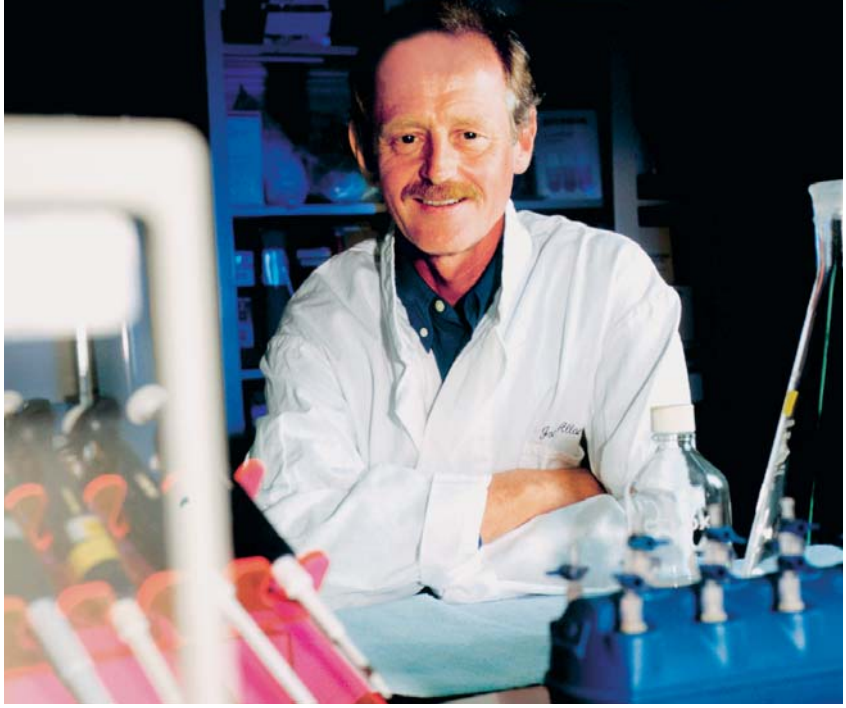
Improving HIV antibodies through genetic engineering. Dr. Paul Zhou has been working to develop a new weapon in the war against HIV by taking an antibody that previously appeared to be ineffective and training it to fight in a better way. This particular antibody is produced by the human immune system to work against gp 41, a glycoprotein on HIV's coating structure that helps it bind and fuse with target immune cells. In its normal function outside the immune cell, this antibody can bind to gp 41, but it is ineffective in disrupting HIV's ability to enter and infect the cell.



Dr. Zhou genetically engineered this antibody to express, or act, on the cell surface. Laboratory tests showed that, with this adaptation, the antibody was highly effective in blocking viral-cell fusion, completely protecting the target immune cells from HIV infection. Also highly encouraging was that the engineered antibody showed broad inhibitory activity, protecting target cells from infection with all the various subtypes of HIV with which they were challenged. Further tests conducted in collaboration with Dr. Jonathan Allan at SFBR and Dr. Jason Kimata at Baylor College of Medicine revealed that this same antibody showed activity in preventing the spread of HIV by blocking the uptake of HIV by dendritic cells, a specialized type of cells that are believed to enhance the spread of infection. These investigations are very encouraging, and it is Dr. Zhou's hope that continued research with this improved antibody might eventually lead to an effective new therapy for treating HIV.

Combining vaccine approaches. In the past several years, a new strategy that uses a harmless human adenovirus containing one of the genes of HIV has been developed as a candidate vaccine. In collaboration with scientists at the National Institutes of Health, Dr. Krishna Murthy and his research team have evaluated an adenovirus HIV vaccine in the chimpanzee model. Administration of the vaccine resulted in the induction of a persistent and strong response by T cells, a type of white blood cell, but no antibodies to HIV were induced. However, researchers found that additional vaccination with gp 140, a protein derived from the outer coat of HIV, was capable of correcting this problem and induced high levels of antibodies to HIV. Dr. Murthy's studies suggest that a combination of both types of vaccines will be essential to preventing HIV infection.

Genetic influence on susceptibility to HIV and AIDS. Dr. Murthy also has been involved in collaborative studies with scientists at the University of Texas Health Sciences Center at San Antonio, and this research team recently identified a correlation between people's genetic susceptibility to HIV/AIDS and the number of copies they carry of a gene that codes for a protein known as CCL31 chemokine. This chemokine has potent suppressive activity against HIV, and study results showed that individuals carrying a lower number of copies of the gene showed increased susceptibility to HIV infection and subsequent progression to AIDS. On the other hand, a higher number of copies of the gene led to



resistance to HIV infection and slower progression to disease. Interestingly, chimpanzees have been shown to resist progression to AIDS following exposure to HIV. One of the reasons is that they possess an even higher number of copies of the gene for the chemokine.

Clues surface regarding the natural resistance of African monkeys. AIDS has its origins in African monkeys. However, unlike humans, these monkeys do not develop disease from infection with SIV, the simian version of HIV. Uncovering how these monkeys resist disease may lead to new treatments against AIDS in humans and has been a major focus of Dr. Jonathan Allan's laboratory.

More than 50 percent of African green monkeys carry SIV in the wild and have high levels of the virus circulating in their blood. Therefore, it appears that their immune system is not responsible for blunting disease. So what does, in fact, give them their natural protection?

Studies in Dr. Allan's laboratory have revealed that these monkeys prevent the destruction of T cells (immune cells targeted by HIV and SIV) by limiting the number of target cells used by SIV to replicate. In a person or animal infected with the AIDS virus, cell surface receptors used by immune cells to communicate and function in defending the host from foreign invaders are commandeered by the virus and used to gain entrance into the cell, ultimately killing the cell. African green monkeys appear to thwart the virus by producing only low levels of these receptors, and in response to infection, they further downregulate these cellular molecules to limit the spread of infection. Further studies by Dr. Allan are directed toward understanding the molecular basis for these host differences that play an important role in determining disease outcome.

Correcting a misunderstanding about the pathogenesis of HIV. One of the greatest challenges in fighting HIV and AIDS is that scientists still lack a sufficient understanding of the pathogenesis of this deadly virus. Much of Dr. Luis Giavedoni's research focuses on helping scientists improve this understanding, and in 2004, experiments conducted by his laboratory corrected a common misperception among AIDS researchers. CD154, one of several molecules produced on the surface of immune cells called CD4+ T cells, is important for the regulation of a person's immune response. Because scientific observations have

shown that this molecule's activity is disrupted in people and animals infected with the AIDS virus, it was suspected that HIV and its simian counterpart, SIV, impair the function of this molecule and thereby cause immunodeficiency in infected individuals. However, Dr. Giavedoni showed that when one group of rhesus monkeys was inoculated with a recombinant virus that expresses CD154, the animals did not show any significant differences in the quality or quantity of their immune response compared to animals inoculated with a recombinant virus that does not express CD154. This indicates that the level of CD154 expression is not in fact related to the deficient immune response observed in patients with HIV infection.

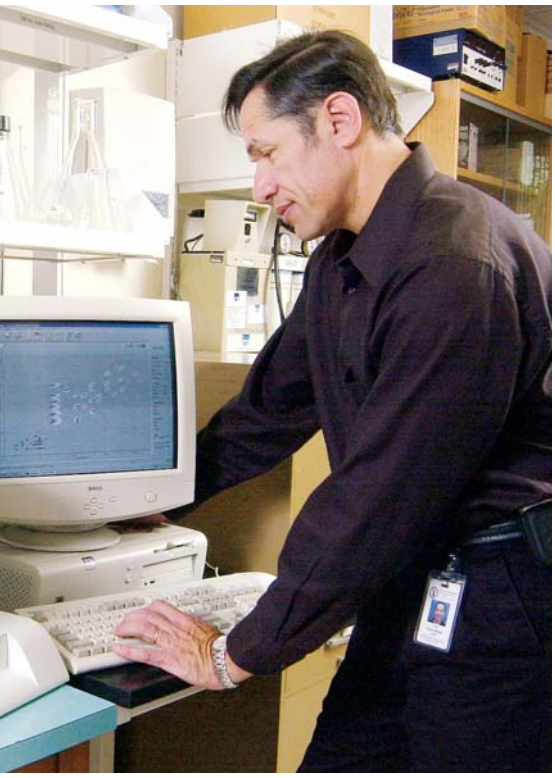
Hepatitis C

Hepatitis C virus (HCV), which chronically infects approximately 200 million people worldwide, causes liver inflammation and chronic disease known as hepatitis, ultimately leading to liver cancer in 20 percent of infected individuals and end-stage liver disease in others, who require liver transplantation.

Dr. Krishna Murthy is involved in collaborative studies with two groups of scientists from the National Institutes of Health to develop an HCV vaccine. These studies, which follow two different vaccine strategies, are being tested in the chimpanzee model to determine their efficacy. Like humans, chimpanzees can be infected with hepatitis C, but unlike humans, they do not progress to liver disease, making them an ideal model for testing potential HCV vaccines.

In one of the approaches under investigation at SFBR, chimpanzees were vaccinated with a non-infectious virus-like particle that structurally resembles HCV. In the other strategy, chimpanzees were first vaccinated with a DNA vaccine containing selected genes of HCV, and then with a mixture of HCV proteins. All vaccinated animals developed T-cell and antibody responses specific to HCV. Studies are now underway to determine whether these vaccine strategies will prevent infection with the virus.

The HCV program led by Dr. Robert Lanford is a component of one of the four national Hepatitis C Cooperative Centers – the Southeastern Hepatitis C Cooperative Center – which also includes components at the University of Texas Medical Branch at Galveston and Johns Hopkins School of Medicine. This program involves molecular studies on the replication of HCV replicons in tissue culture cells as well as animal studies using the chimpanzee model of HCV infection. Dr. Lanford is investigating the basis of these animals' natural protective immunity, and he is analyzing HCV-induced changes in liver gene expression as he assists in national



efforts to develop better therapies and potential vaccines for HCV. He also continues to collaborate with many of the nation's top pharmaceutical companies to test potential new treatments and vaccines they have designed, and he is hopeful that a cure for hepatitis C is within reach.

In 2004, Dr. Lanford's work gained national attention as a result of findings he and his collaborators published in the *Journal of Virology*. This article offered the first evidence that a vaccine against all strains of hepatitis C should be possible, showing that chimpanzees that previously cleared infection with one strain or genotype of the virus show protective immunity to multiple, highly divergent strains. While an actual vaccine could still be several years away, this finding is significant because scientists had previously thought that prior infection with HCV only produced immunity to the specific strain with which one had been infected.

Hepatitis B

The hepatitis B virus (HBV) poses a major global health problem, with an estimated 350 million chronic carriers worldwide, including 1.2 million people in the United States. The efficacious vaccine now given to U.S. children will significantly curtail new infections, but it will not help people already chronically infected.

Chronic HBV infections often progress to cirrhosis and liver cancer and are among the top 10 causes of death worldwide. Although several antiviral medications are currently FDA-approved to treat HBV, these treatments only suppress viral replication. They do not cure individuals of the infection, and they must be taken for life. Eventually, viral resistance renders them useless. Therefore, a great need exists to create better antiviral strategies to eliminate the chronic-carrier state.

Dr. Robert Lanford and his research team have recently identified a short synthetic peptide that mimics the viral envelope and blocks HBV infection by competing with the virus for the unknown viral receptor. Not only does this research provide new opportunities for the development of novel antivirals that block infection, but Dr. Lanford also is now using the peptides to search for the cellular receptor for the virus.

A number of laboratories have been searching for the HBV receptor for several decades, but to date, it remains elusive. One of the major obstacles to identification of the receptor is the lack of a tissue culture system. Dr. Lanford has used his expertise in the cultivation of primary primate hepatocytes to develop a tissue-culture system that will aid in the identification of the receptor. Rather than work directly with HBV, his studies involve the use of a defective hepatitis virus

(HDV) that requires the HBV envelope proteins for transmission and cellular entry. This surrogate system can be manipulated in the laboratory much more readily than HBV, but since it uses the same cellular receptor as HBV, it can be used to search for the HBV receptor.

In 2004, Dr. Lanford's group defined a short segment of the HBV envelope protein as being necessary for interaction with the unknown receptor. The team synthesized short peptides that mimic portions of the envelope protein and demonstrated that one of the peptides competed with the virus for the receptor and thus blocked infection. Using a reductionist strategy, they defined a peptide of 15 amino acids in length that can block infection. One of the novel aspects of the peptide is that it required modification by myristylation (a fatty acid added to the amino terminus of proteins) for biological activity. Dr. Lanford and his research team are now using this peptide as the bait in their "fishing expedition" for the receptor.

Emerging and exotic viruses

Emerging viruses are those viral pathogens that exist in neighboring countries and threaten to become prevalent in the United States. One such virus under investigation at SFBR, dengue, already has been detected in some South Texas border communities.

Dengue. Dengue is the most common mosquito-borne viral disease of humans. The spread of both the virus and the mosquitoes that can carry it has led to the resurgence of epidemic dengue fever – a self-limited flu-like syndrome – and the emergence of dengue hemorrhagic fever – severe dengue with bleeding abnormalities – in urban centers of the tropics.

There are no animal or laboratory models of dengue disease, but indirect evidence suggests that dengue viruses vary in virulence, including their pathogenicity for humans and epidemic potential. At SFBR, Dr. Rebeca Rico-Hesse and her research team have developed two assay systems in which to measure differences in virus replication that correlate with potential to cause hemorrhagic dengue and increased virus transmission. These assay systems use human dendritic cells and *Aedes aegypti* mosquitoes.

Infection and growth experiments conducted in Dr. Rico-Hesse's laboratory showed that dengue serotype 2 viruses seen in Southeast Asia, which can cause dengue hemorrhagic fever epidemics, can out-compete American genotype viruses that cause dengue fever only. This implies that the Southeast Asian genotype viruses will continue to displace others, causing more hemorrhagic dengue epidemics.

Detecting SARS and other deadly agents. Severe acute respiratory syndrome (SARS), a viral respiratory illness caused by a coronavirus, was first reported in Asia in February of 2003. From there, it quickly spread within a few months to more than two dozen countries in other parts of Asia, North and South America, and Europe before it was contained. By that time, according to the World Health Organization, a total of nearly 8,100 individuals contracted the illness, and 774 people died from their infection.

Because symptoms of SARS can initially be confused with the flu and other illnesses, improved methods are needed for SARS detection and diagnosis. This is one of the goals of Dr. Andrew Hayhurst's laboratory.

In his first year at SFBR, Dr. Hayhurst has developed a rapid and sensitive assay for the SARS virus. The gold standard for virus identification is isolation, purification and visualization combined with immunochemical identification and nucleic acid sequencing. Since this battery of tests is time-consuming, expensive and not amenable to high throughput, current laboratory efforts typically aim at first to employ one or two components to give a strong indication of the presence of a particular virus. In the past, immunochemistry was used to detect virus in a way that first used suitably immobilized antibodies to capture virus and then used suitably labeled antibodies to bind and reveal that captured virus. The assay was nicknamed a "sandwich" assay, because the antibodies are akin to layers of bread while the virus forms the sandwich filling. However, sensitivities of this method were never better than approximately one million viruses per milliliter because of the poor quality of the antibodies and the lack of technological know-how. As nucleic acid amplification using PCR and RT-PCR appeared, with detection limits down to a single virus particle, the humble sandwich essentially became obsolete. However, RT-PCR is still not a clinical tool because it is prone to errors, requires several hours of sample preparation, is not easily adapted to high throughput, and is still very expensive.

For these reasons, Dr. Hayhurst decided to take a fresh look at old "sandwiches." By using state-of-the-art recombinant-antibody-technology methods, he and his research group have engineered exceptionally high-quality antibodies that perform very well in the standard sandwich assay format. Currently, limits of detection are between 100 and 10 virus particles with an inexpensive one-hour assay that is capable of high throughput. Eventually, it is envisioned that this assay will provide clinicians' offices with a simple, rapid and robust diagnostic test for SARS. The methodologies that have been developed as a result of this work are also being applied to other emerging viruses handled in the Foundation's biosafety level four (BSL-4), maximum-containment laboratory.

Biodefense

Dr. Jean Patterson's team continues to focus on research related to biodefense, a role that has expanded since the Foundation's designation in 2003 as part of the NIH-sponsored Region VI Center of Excellence for Biodefense and Emerging Infectious Diseases. The University of Texas Medical Branch at Galveston is the lead organization in this consortium that unifies the scientific efforts, resources and expertise of 16 member institutions in Texas, Arkansas, Oklahoma, New Mexico and Louisiana. The unique resources of SFBR were critical to the Foundation's ability to secure the Biosafety Level 4 Core and the Small Animal Core for the consortium.

Even before the anthrax attacks of October 2001, Dr. Patterson was working in collaboration with Dr. Brent Iverson at the University of Texas at Austin on an antibody to treat the deadly toxins released by anthrax bacteria during infection. Although antibiotics can be used to clear a patient of infection with the bacteria, there currently is nothing that can be used to eliminate these deadly toxins and thereby save the life of a patient with late-stage anthrax infection. Therefore, the success of this UT-designed antitoxin would be a significant, life-saving breakthrough in the nation's biodefense efforts.

Research conducted at SFBR originally showed that this high-affinity antibody was suc-

cessful in protecting rats from anthrax toxin. Now Dr. Patterson's group is testing this antidote in true anthrax spore challenges with guinea pigs and rabbits, two animal models exquisitely sensitive to anthrax. Dr. Patterson also continues to collaborate with Dr. Karl Klose at the University of Texas at San Antonio on the development of an oral vaccine against multiple biological weapons, including anthrax.

Another area of Dr. Patterson's research is being done in collaboration with Dr. Igor Lukashevich at the Institute of Human Virology at the University of Maryland on the development of a live-attenuated vaccine against the Lassa virus, which causes Lassa fever. Lassa is an animal-borne virus endemic to West Africa, where it infects between 300,000 and 500,000 people and has a mortality rate that ranges from 10 to 20 percent. Research conducted at SFBR by Dr. Patterson's laboratory has shown this vaccine to be effective in guinea pigs. If further tests with nonhuman primates show similar success, this vaccine would be eligible to move into human clinical trials.

Dr. Patterson also continues to serve as an advisor to the Department of Homeland Security's National Biodefense Analysis and Countermeasures Center (NBACC). One of her roles in this position is to help NBACC generate likely scenarios related to a biological attack. Her laboratory recently began new research for the Federal Bureau of Investigation (FBI), with whom Dr. Patterson is working to further characterize the anthrax that was used in the bioterror attacks of 2001. She also will be working closely with the Department of Homeland Security on several future projects.

Immunological studies

Cytokines and chemokines are mediators of the immune system that play a crucial role in intercellular signaling, or communication between cells, and in the recruitment of immune cells to inflammation sites. The identification of various cytokines and chemokines that are present at normal or abnormal levels provides immunological markers that serve as indicators of the type or progression of disease within an individual. In research with nonhuman primates, the identification of these molecules is crucial for the understanding of complex physiological and pathological mechanisms that occur in these species, and to help determine whether these mechanisms function similarly in humans. That understanding would help determine whether a particular animal serves as a true model for certain human diseases.

Previously, studies with nonhuman primates required individual blood samples for tests on each type of cytokine or chemokine under investigation. However, in 2004, Dr. Luis Giavedoni and his research team identified reagents, or assay systems based on new combinations of antibodies, that allow for the identification of more than 20 cytokines and chemokines in a single sample. These reagents will provide a useful resource for scientists working with nonhuman primates in their research on a broad variety of diseases.

Separate research was conducted by Dr. Giavedoni in collaboration with the research group of Dr. Peter Nathanielsz, previous director of the Center for Women's Health Research at New York University and now a member of the faculty at the University of Texas Health Science Center at San Antonio. Together, these research teams demonstrated that the same types of immunological changes that are observed in pregnant women are also seen in pregnant baboons. Although a person's immune system typically rejects foreign objects within the body, a woman's immune system does not normally cause the rejection of a pregnancy or interfere with the fetus' immune system; however, various immunological changes are still observed in the mother. Through their observation of these same changes in pregnant baboons, Drs. Giavedoni and Nathanielsz have increased the validity of the baboon as a valuable model for pregnancy studies.

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(as of December 2004)

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Robert E. Lanford, Ph.D.
Krishna K. Murthy, D.V.M., Ph.D.
Rebeca Rico-Hesse, Ph.D.

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Luis D. Giavedoni, Ph.D.
Paul Zhou, Ph.D.

Assistant Scientists

David W. Martin, Ph.D.
Andrew Hayhurst, Ph.D.

Staff Scientists

Ricardo Carrión, Ph.D.
Vida L. Hodara, Ph.D.

Postdoctoral Scientists

Justin R. Anderson, Ph.D.
Dennis Bente, D.V.M.
Seung Jae Lee, Ph.D.

DEPARTMENT OF PHYSIOLOGY AND MEDICINE

Research in the Department of Physiology and Medicine focuses on two major areas of biomedical research: cardiovascular diseases and cancer drug discovery.

In these research efforts, departmental faculty collaborate extensively with investigators from other departments at SFBR as well as at other institutions throughout the United States and around the world. Results of their investigations in 2004 have led to several new advances in biomedical research.

ASSOCIATE SCIENTIFIC DIRECTOR & ACTING CHAIR

Robert E. Shade, Ph.D.

Cancer drug discovery

Dr. Susan Mooberry leads a cancer drug discovery program at SFBR with the aim of finding new drugs that may be useful in the treatment of cancer. In the past year, her laboratory identified several different classes of natural and synthetic compounds and evaluated them for activities that may predict anticancer effects.

One approach used in this research is to identify compounds that act on cellular structures called microtubules. Microtubules are used by cells to guide genetic material into the two new daughter cells during the cell division process. Disruption of microtubule function inhibits cell division and signals cancer cells to initiate apoptosis, or cellular death. Disruption of microtubule function by stabilizing microtubules is an effective anti-cancer mechanism. Microtubules need to be dynamic for successful cell division, so when microtubules are stabilized, the cell recognizes that something is inherently wrong and initiates its own destruction.

The first microtubule stabilizer identified, Taxol, is currently used to treat several types of cancer, and the search continues for new drugs that share its same mechanism of action, particularly for the treatment of Taxol-resistant tumors. A new microtubule stabilizer, laulimalide, was discovered through Dr. Mooberry's screening program. Found in extracts from a marine sponge, laulimalide has been shown to have promising activities against cancer cells in tissue culture. Unfortunately, it has chemical characteristics that cause it to be unstable. Laulimalide analogs designed for chemical stability are expected to be superior to the natural product for antitumor actions.

In collaboration with Dr. Paul Wender's research program at Stanford University, Dr. Mooberry's laboratory evaluated several new synthetic laulimalide analogs that were designed to have superior chemical stability. Experiments showed that two of these analogs have effects identical to the parent compound, while several others exhibit-

ed slightly different mechanisms of action. Now the information derived from these recent studies will be used to design a third generation of analogs with improved cytotoxic properties. The promising results of this collaborative research were published in the *Proceedings of the National Academy of Sciences of the United States of America*, and this prestigious journal recently recognized the publication as one of the top 100 journal articles electronically accessed during the year after its publication.

Other recent efforts in Dr. Mooberry's drug discovery program include a collaboration with Dr. Milton Brown at the University of Virginia to identify synthetic compounds with activity against breast cancer cells. In other collaborations with Dr. Phillip Crews at the University of California, Santa Cruz, and Dr. Yoichi Nakao at the University of Hawaii, she evaluated compounds derived from marine organisms such as sponges, mollusks and deep-water fungi and identified their mechanisms of action.

Cardiovascular diseases

Atherosclerosis research. Individuals show considerable variability in the response of their blood cholesterol levels to dietary fat and cholesterol content. In fact, high- and low-responding individuals have been identified within both human subjects and animal species used to study cholesterol metabolism. At SFBR, selectively bred strains of laboratory opossums also show extreme variability in diet-induced changes in blood cholesterol and fat levels that are similar to the extreme variation found in humans. Previous studies conducted by Dr. Rampratap Kushwaha's program have shown that the

effect of dietary fat and cholesterol on blood cholesterol levels in these animals was due to one major gene. Studies conducted during 2004 were designed to determine whether the higher blood cholesterol levels found in the high-responding opossums on a high-fat, high-cholesterol diet could be explained by a mechanism that promotes higher absorption of dietary cholesterol in high- versus low-responding animals.

High-responding opossums on a high-fat, high-cholesterol diet absorbed 61 percent of the dietary cholesterol, but the low-responding opossums absorbed only 31 percent. In addition, liver cholesterol levels were three times higher in the high responders. Measurements were made for an enzyme – acyl-coenzyme A:cholesterol acyltransferase (ACAT) – that is involved in intestinal cholesterol absorption as well as absorption of blood cholesterol into liver tissue. There was no association of intestinal ACAT levels with blood cholesterol levels in the high responders, but there was a significant association between liver ACAT activity and blood cholesterol. These studies suggest that dietary cholesterol absorption is a major determinant of diet-induced increased blood cholesterol levels in high-responding individuals. Additional studies are needed to explain the link between liver ACAT activity and increased absorption of dietary cholesterol.

Doctoral Staff
(as of December 2004)

Acting Chair
Robert E. Shade, Ph.D.

Senior Scientist Emeritus
Henry C. McGill Jr., M.D.

Scientist
Rampratap S. Kushwaha, Ph.D.

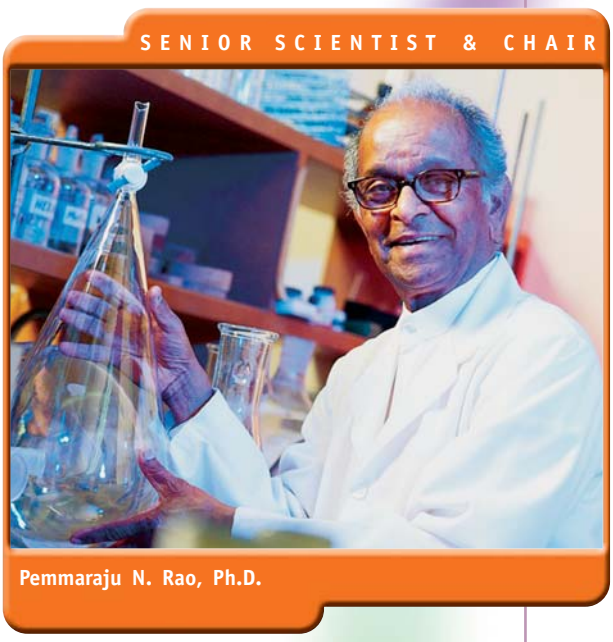
Associate Scientist
Susan L. Mooberry, Ph.D.

Salt and water metabolism in blood pressure regulation. The relationship between dietary sodium or salt content and blood pressure regulation is being investigated in baboon studies conducted by Dr. Robert Shade's research program. In a previous collaboration with Dr. Candace Kammerer, a former SFBR faculty member in the Genetics Department, Dr. Shade surveyed several biochemical and hormonal characteristics of the pedigreed baboon colony that were known to be risk factors for the development of hypertension in humans. One of the factors measured, red blood cell sodium-lithium countertransport (SLC), is well established as a biochemical marker of inherited dietary-salt-induced human hypertension. Very little is known in regard to the physiological mechanisms implicated by high SLC and hypertension because, previous to this study, there were no animal models that replicated the SLC values found in human populations. However, this baboon genetics study found that baboons have SLC values identical to those reported for human populations, and Dr. Kammerer's genetic analysis of the data indicated that a single major gene accounted for approximately 60 percent of the variation in SLC levels in the pedigreed baboons.

In collaboration with Dr. J.R. Haywood at Michigan State University, Dr. Shade received funding from the National Institutes of Health to challenge baboons with high and low SLC values in an attempt to discover the mechanism or mechanisms that produce an increase in blood pressure in high-SLC individuals consuming a high-salt diet. The first set of these experiments was completed in 2004 and involved feeding high-SLC and low-SLC baboons three levels of dietary salt for four weeks. This study found that a steroid hormone that controls kidney salt excretion, aldosterone, responds appropriately to changes in dietary salt content in low-SLC baboons but remains elevated in high-SLC baboons placed on a high-salt diet. Since high aldosterone levels promote salt retention by the kidneys, the link between high SLC and sodium-sensitive blood pressure may be a genetically induced disruption in the control of aldosterone secretion.

DEPARTMENT OF ORGANIC CHEMISTRY

In April 2004, the Department of Organic Chemistry entered into year three of a five-year contract as The Synthetic Chemical Facility for the Contraceptive Development Branch (CDB) of the National Institute of Child Health and Human Development, National Institutes of Health.



Pemmaraju N. Rao, Ph.D.

This marks the 28th consecutive year that the department has served in this capacity through a number of contracts.

These contracts were awarded on a competitive basis, and the Department of Organic Chemistry has been consistently recognized as the premier research group in the nation for steroid synthesis. Over the years, Dr. P.N. Rao and his research staff have developed synthetic methods for the production of hundreds of steroids and other compounds. These compounds have been investigated for developing safer and more effective methods of contraception as well as treatment for a variety of reproductive disorders.

Current projects and areas of interest include:

Selective progesterone receptor modulators

The potential applications of selective progesterone receptor modulators involve contraception as well as treatment of endometriosis, progesterone-dependent tumors, uterine fibroids, premenstrual syndrome and adverse symptoms of menopause.

The antiprogestin known as CDB-4124 was conceived and synthesized in Dr. Rao's laboratories. Subsequent biological testing indicated this analog exhibited three times the antiprogestational activity of the parent compound with significantly decreased side effects. This compound and several other derivatives are the subject of a pending U.S. patent titled "21-Substituted Progesterone Derivatives as New Antiprogestational Agents." In July 2004, the United States Patent and Trademark Office (USPTO) issued U.S. Pat. No. 6,768,014 titled "Process for the Preparation of 17α-acetoxy-11β-[4-N,N-(dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9-diene-3,20-dione, Intermediates Useful in the Process, and Processes for Preparing such Intermediates." This patent covers improved methods for

the synthesis of CDB-4124 developed in Dr. Rao's laboratories.

Under the trade name Progenta™, CDB-4124 has been licensed to Zonagen Inc. for development in the treatment of uterine fibroids, endometriosis as well as progesterone-dependent breast tumors. In June 2004, Zonagen Inc. initiated a European Phase I/II study of Progenta™ to assess its safety and efficacy for the treatment of uterine fibroids. Preliminary results released by Zonagen Inc. in September and November 2004 indicate that Progenta™ is well tolerated with no negative side effects and achieved statistically significant reduction in fibroid size compared to a control group. Progenta™ also performed favorably when compared to a positive control group using Lucrin®, a GnRH agonist commonly administered for the treatment of fibroids. Final results of this study are expected to be released in early 2005.

In September 2004, Zonagen Inc. gave a presentation at the 12th International Congress of Endocrinology in Lisbon, Portugal titled "Progenta™ as a Potential New Approach in the Treatment of Breast Cancer." The data presented indicated Progenta™ was superior in reducing the proliferation of tumor cells when compared to other drugs with similar modes of action and in the same chemical class.

Male contraceptives

One promising approach to controlling male fertility is through the administration of a single agent that is both antigonadotropic and androgenic. A drug that is antigonadotropic blocks gonadotropic-releasing hormones, resulting in azoospermia, or zero sperm count, to inhibit conception. An undesired side effect of an antigonadotropic agent, however, is the reduction of testosterone production in the testes, which in turn lowers the male's libido. Consequently, it is necessary to supplement antigonadotropic medication with an androgenic drug to restore normal libido.

Dr. Rao and his research team have been highly successful in developing high-potency, long-acting testosterone derivatives for this purpose. It has been reported that several derivatives of 19-nortestosterone are in fact more potent than

testosterone with a longer duration of action. Over the past year, Dr. Rao's group has synthesized several novel derivatives of 19-nortestosterone that will be tested as potential male contraceptives.

Doctoral Staff
(as of December 2004)

Senior Scientist and Chair
Pemmaraju N. Rao, Ph.D.

Novel 2-methoxyestradiol compounds with anticancer activity

2-Methoxyestradiol is a natural metabolite of estradiol devoid of estrogenic or tumor-promoting activity *in vivo* (in mouse models). In 1989 it was discovered that 2-ME2 inhibits the cellular machinery involved in replicating cancer cells, specifically microtubules, the intracellular target of the well-known anticancer drug Taxol™. In addition, 2-ME2 has been demonstrated to act as an antiangiogenic agent that prevents the growth of new blood vessels required to nourish tumors. Upon learning these findings, the Department of Organic Chemistry initiated a program to investigate the potential anticancer application of existing and newly synthesized 2-ME derivatives. The department collaborated with Dr. Susan Mooberry in SFBR's Department of Physiology and Medicine to have these compounds tested for antiproliferative activity against breast and ovarian cancer cells. Three of the analogs were found to have promising activity.

The compounds and methods developed in Dr. Rao's laboratories for the synthesis of these analogs are the subject of U.S. Patent No. 6,593,321 titled "Novel 2-Alkoxyestradiol Analogs with Antimitotic Activity."

In February of 2004, the Department of Organic Chemistry entered into a 12-month sponsored research agreement with Entremed Inc. of Rockville, Md., titled "Synthesis of New 2-Methoxyestradiol Analogs." Under this contract, Dr. Rao and his research team have synthesized several new 2-ME2 analogs for biological evaluation by Entremed Inc. Preliminary results from *in vitro* testing (in cell cultures) indicate three new compounds with promising results.

DEPARTMENT OF COMPARATIVE MEDICINE

While some specific research questions may be adequately addressed using cell cultures, tissue studies or computer models, research with animals continues to be critical for the advancement of human health.

CHAIR

K. Dee Carey, D.V.M., Ph.D.

Disease processes are typically complex, involving multiple physiological processes and multiple organ systems. That is why many research questions can only be answered through detailed study of a whole living system, and it is why alternative research tools such as computer models can complement but not fully replace research with animals. This also explains why, during the past century, virtually every major advance in medical knowledge and treatment involved research using animal models.

At SFBR, the Department of Comparative Medicine plays a critical role in enabling these medical advances, as its staff and resources are dedicated to the outstanding care of the Foundation's animal colonies and to providing skilled support for humane and appropriate research that relies on these animals. Researchers in the department, including one SFBR scientist and three adjunct scientists, also lead their own investigations involving animal models of human health and disease.

The monumental efforts of the department require the dedication and expertise of a large, highly qualified staff. Seven veterinarians, a veterinary pathologist, one doctoral-level scientist, and 94 technicians and animal caretakers are charged with the care of more than 5,800 nonhuman primates, including approximately 3,700 baboons, 1,800 macaques, 235 chimpanzees, 200 marmosets, and more than 100 nonhuman primates of other species. They also provide care for the nearly 3,000 other animals at the Foundation, including a large colony of laboratory opossums.

In addition to animal care, this staff performs a wide variety of observational procedures and research protocols in support of research projects conducted both by SFBR scientists and scientists from other collaborating institutions from throughout the United States and abroad. The group also conducts research concerned with health problems in domestic nonhuman primate colonies and searches for spontaneous nonhuman primate models of human disease.

A critical function of the department is its work to ensure that SFBR programs and facilities are in compliance with state and national regulations, federal regulatory agencies, and voluntary accrediting agencies. Since 1973, SFBR has voluntarily been accredited by the Association for the

Assessment and Accreditation of Laboratory Animal Care, International (AAALAC, Int.), an agency that assures high-quality standards for the care and use of laboratory animals.

Expert staff members play valuable roles

Veterinary staff. The overarching responsibility of the Department of Comparative Medicine is to provide high-quality care for all of the Foundation's research animals and to offer research support by an expert veterinary staff that cares about the animals and their well-being. The Foundation's eight veterinarians are a highly qualified group, with a combined total of more than 110 years of experience in nonhuman-primate veterinary medicine. They provide a wide range of special skills and knowledge, including open and endoscopic surgery, anesthesia, diagnostic procedures such as x-ray and ultrasound, clinical diagnosis and disease management, specialized nursery care of infants, and anatomic and clinical pathology. The veterinary staff meets regularly to discuss interesting cases, problems and solutions to those problems. The veterinarians are encouraged to be alert to new disease problems that occur among captive nonhuman primates and to identify spontaneous diseases that provide models of human disease.

The veterinary technical and animal-care staff includes 12 supervisors, 39 technicians and 43 animal caretakers. Several members of the staff have been at the Foundation for more than 30 years. They are skilled in providing support before, during and after surgical procedures. Senior technical staff, who work under the supervision of a responsible veterinarian, are responsible for the daily operations of the Foundation's two hospitals and three clinics. They admit animals, develop clinical histories, order tests, and treat animals according to the veterinarian's medical orders. The supervisor in charge of reproductive assessment is skilled in using sonography to estimate the gestational age of the nonhuman primate fetus – a procedure essential to the Foundation's research program focused on lung disease of the premature baboon, the only animal model available to study the chronic lung disease that affects many premature human infants. Many of the animal-care and technical staff responsible for the chimpanzee colony also have been at SFBR for many years, and most know each animal and its unique personality. This skilled, experienced staff is dedicated to the well-being of the animals for which they provide care.

Environmental enrichment program. Environmental enrichment is a critical and mandated component of every facility that maintains nonhuman primates. At SFBR, a behavioral scientist directs a staff of five technicians in a program of environmental enrichment for all of the Foundation's nonhuman primate colonies as well as its other animals. This group devises new enrichment procedures, orients animal caretakers regarding behavioral issues, and is available for consultation when behavioral problems occur among animals.

Animal records. All the work of providing daily care, health care, environmental enrichment, and research support must be documented. For this purpose, the Department of Comparative Medicine has worked with the division of Biostatistics and Scientific Computing (BSC) to develop a Computerized Animal Management Program (CAMP). CAMP is a database for maintaining all the records necessary for the provision of excellent health care and research support, as well as to maintain compliance with state and federal agencies and voluntary accrediting agencies. BSC has developed several applications designed for PDAs specifically for the department's use. These provide the staff with efficient methods of capturing information and electronically downloading

it to CAMP. Examples of information captured are daily observations of all animals, monitoring the reproductive changes in the Foundation's breeding colonies, and recording behavioral observations.

Animal colonies enable life-saving and life-improving research

The majority of nonhuman primates at SFBR are represented in the colonies of chimpanzees, baboons, rhesus and cynomolgus monkeys, and marmosets. Chimpanzees are the only animal model that can be used for preclinical tests of some of the new pharmaceuticals that are engineered for use in humans. They were the first animal model for AIDS and serve as the primary animal model for hepatitis C and potential drugs to treat this disease.

Baboons served as an important animal model in the early history of SFBR for cardiovascular disease and for testing contraceptives. In the early 1970s, the pedigreed baboon breeding colony was initiated to investigate genetic and pathophysiologic factors of cardiovascular disease. Today, with the census of about 2,000 animals – of which about half have been genotyped – the colony is a powerful tool in the search for genes responsible for factors associated with cardiovascular disease, obesity, diabetes, epilepsy, Chagas disease, and other chronic diseases. In addition, a colony of aged animals has been maintained so that scientists can search for genes associated with age-related changes in these geriatric baboons.

A breeding colony of Indian-origin Specific Pathogen Free (SPF) rhesus monkeys was acquired in the late 1990s. These animals are the model of choice for studying AIDS, vaccine therapies to prevent it, and drugs to treat it.

The department maintains a small group of marmoset monkeys to support research done by the Department of Virology and Immunology on infectious diseases. When Dr. Suzette Tardif joined the Southwest National Primate Research Center as its associate director, she brought a colony of marmosets with her. Her research is focused on aspects of marmoset reproduction and pregnancy; however, she is working to extend the use of marmosets into the areas of obesity and aging.

The number of other, non-primate animals at the Foundation are represented mainly by the large

colony of South American opossums. These animals provide a valuable model for genetic analyses of dietary-induced hypercholesterolemia, as well as for research related to cancer, the repair of spinal cord injury, and other maladies.

Nonhuman primate models of chronic human disease

Old World nonhuman primates – primates of African and Asian origin – are genetically closely related to humans and develop most of the same chronic diseases as humans. The early changes that occur as these diseases progress are interesting to scientists because it is at these early stages that interventions are sought that might prevent or decelerate disease development. The Foundation's veterinary staff works with scientists at SFBR and local and national universities to identify nonhuman primate models of chronic human diseases. A description of four such diseases follows.

Endometriosis. Endometriosis is a condition in women in which the tissue that normally lines the uterus (endometrium) grows in other areas of the body, causing pain, irregular bleeding, and frequently infertility. Veterinarians at SFBR have identified the lesions of endometriosis in baboons. These lesions in baboons are similar to those in women and are associated with infertility. The identification of endometriosis in the baboon will provide an animal model to test therapies meant for the human market.

Gastroesophageal reflux disease (GERD). Gastroesophageal reflux is the term used to describe a backflow of acid from the stomach into the esophagus. Almost everyone experiences gastroesophageal reflux at some time. The usual symptom is heartburn, most commonly occurring after a meal. In some individuals reflux is frequent or severe enough to cause more significant problems and to be considered a disease. GERD may lead to esophageal constriction and discomfort in swallowing, and at its worst, it can cause precancerous lesions in the lower esophagus. The veterinary and behavioral staffs have identified animals at SFBR that regurgitate. Gastroscopic examination demonstrated an inflamed lower esophagus, and biopsy and histological examination revealed lesions of the mucosa similar to those seen in humans. The iden-

tification of GERD in baboons will provide a naturally occurring model to study behavior and pathophysiologic changes associated with GERD, as well as an animal model to test drug and biomedical device therapies.

Epilepsy. Epilepsy is a brain disorder that occurs when the electrical signals in the brain are disrupted. This change in brain signals leads to a seizure. For a number of years, SFBR veterinarians have identified a few animals in the pedigreed baboon colony that are epileptic and have seizures. Consequently, the veterinarians have worked with neurologists to characterize baboon epilepsy and to demonstrate that the disease occurs in families of baboons. A member of the Genetics Department has teamed up with the group to examine genetic components of the disease.

Obesity and type 2 diabetes. Like people, baboons can become obese, and some of these animals become insulin resistant and progress to type 2 diabetes. Veterinarians at SFBR have worked with scientists in the Department of Genetics to identify and characterize obese and insulin-resistant animals in the pedigreed baboon colony. This allows geneticists to use the extensive pedigrees that have been developed over the past 30 years of breeding these animals to search for genes associated with obesity, insulin resistance and type 2 diabetes.

Research projects

SFBR veterinarians collaborate on research projects conducted by scientists at the Foundation and at outside research institutions throughout the United States and abroad. The following projects exemplify how these diverse research efforts utilize unique aspects of the various animal models at SFBR, as well as the skills and knowledge of the staff who support these projects.

Epilepsy. For more than 30 years, SFBR veterinarians have documented the occurrence of spontaneous epilepsy in the baboon. After several years of work with scientists

in the Department of Genetics and physicians at the University of Texas Health Science Center at San Antonio to characterize the nature of the seizures, the group attained funding from the National Institutes of Health to further characterize the model using electroencephalography and to attempt to identify genes related to epilepsy in humans.

Gene therapy for hepatitis C. Patients who recover spontaneously from acute hepatitis C (HCV) infection exhibit a vigorous response in certain white blood cells (cellular immune response), while those patients with a weak and narrowly focused response remain infected. Would patients chronically infected with HCV clear the infection if the cellular immune response were boosted? Chimpanzees are the only animal model susceptible to HCV. A few chimpanzees remain chronically infected, while some clear the virus. A research project underway at SFBR will combine two viruses to deliver three antigens from the HCV virus in an attempt to enhance the cellular immune response and clear the infection from the chronically infected chimpanzee.

Artificial vertebral discs. While baboons are quadrupeds, they spend a good deal of their time in an upright position, and they are the largest of the commonly available nonhuman primates. The large size and upright position make them one of the best animal models for testing artificial vertebral discs. Discs that will fit small people will fit large male baboons. Because of their upright position, baboons exert many of the same forces on artificial discs as humans would. Scientists' interests are in the biomechanical changes that a disc may impart and in the bio-compatibility of disc material and live tissues.

Obstetrics Pharmacology Research Unit. The onset of pregnancy results in changes in maternal physiology and the metabolism of endogenous compounds as well as administered medications. Drug metabolism in pregnancy is poorly understood, and drug companies are reluctant to examine drug metabolism in pregnancy because of potential risk to the fetus. The National Institute of Child Health and Human Development initiated a program to examine the metabolism of such drugs as anti-epileptic and anti-diabetic medications that women must take during their pregnancy. The institute's program has both a clinical and basic research component. Grants were awarded to four groups in the United States to better understand drug metabolism during pregnancy, including a group from the Obstetrics Department at the University of Texas Medical Branch at Galveston. The Department of Comparative Medicine at SFBR is providing an animal core for the Galveston program and will measure drug metabolism in pregnant baboons prior to the drugs' use in women.

Doctoral Staff

(as of December 2004)

Chair

K. Dee Carey, D.V.M., Ph.D.

Associate Chair
Director, Animal Resources

Larry B. Cummins, D.V.M.

Scientists

Gene B. Hubbard, D.V.M.
Suzette Tardif, Ph.D.

Veterinarians

Kathleen M. Brasky, V.M.D.
M. Michelle Leland, D.V.M.

Assistant Veterinarians

Stephanie D. Butler, D.V.M.
Kristen R. Rohde, D.V.M.

Staff Scientists

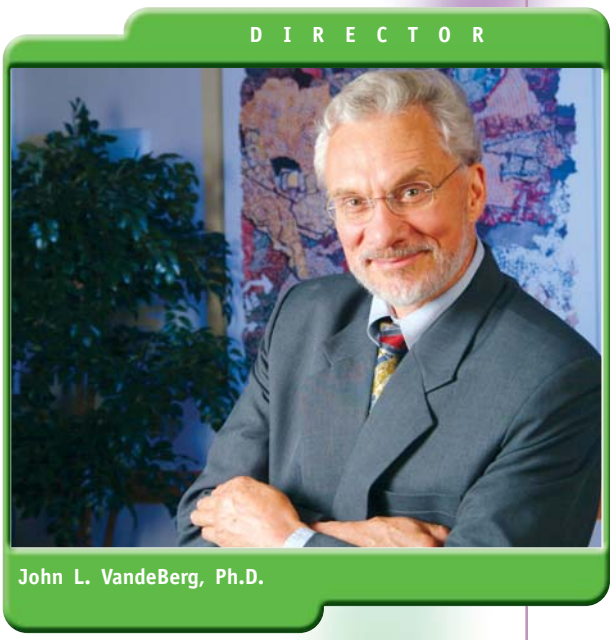
Massimo Bardi, Ph.D.
Christina Grassi, Ph. D.
Jerilyn K. Pecotte, Ph.D.
Karen S. Rice, Ph.D.

Clinical Veterinarian

Melissa A. De La Garza, D.V.M.

SOUTHWEST NATIONAL PRIMATE RESEARCH CENTER

In 1999, when the National Institutes of Health designated SFBR as the country's eighth National Primate Research Center, the Foundation's resources and expertise with nonhuman primates took on an increasingly important role not only in the research efforts of SFBR scientists, but also with those of other scientists and research institutions across the country.



John L. VandeBerg, Ph.D.

The NIH supports the national primate research centers to advance the development and utilization of nonhuman primate models for research on human disease, and each of the eight centers uses its unique combination of resources, infrastructure, animals and expertise in collaboration with scientists throughout the United States as they work with nonhuman primates on studies to benefit human health. In this way, the establishment of the Southwest National Primate Research Center (SNPRC) at SFBR has benefited scientific research at SFBR and far beyond.

The SNPRC base grant, which is funded by a division of the NIH known as the National Center for Research Resources (NCRR), assists the Foundation by providing funds for physical and administrative infrastructure and primate research, for research services that facilitate existing research programs, and for pilot studies that are expected to lead to major new grants. As of December 2004, NCRR also has awarded the SNPRC nearly $11 million in grants toward renovation, improvement and expansion of the Foundation's primate research facilities.

These valuable financial resources have enhanced SFBR's ability to provide its animals with the highest quality of care and housing while expanding important biomedical research programs that rely on its animal colonies. The Foundation is home to approximately 6,000 nonhuman primates, including the largest research colony of baboons in the world. Because of their close similarity to humans in both genetics and physiology, these animals fill a unique and critical role in efforts to understand human health and disease.

Primate center base grant yields largest grant in SFBR history, enables development of new scientific resources

In 2004, NCRR renewed the SNPRC base grant for $27.9 million over the next five years. The largest grant ever awarded to SFBR, the new SNPRC base grant is enabling the development of new scientific resources at the center and further enhancing its ability to serve as a national resource.

A sampling of the new initiatives being funded by the base grant include the following projects:

Primate model for tuberculosis. The SNPRC plans to develop a primate model for tuberculosis, creating a valuable new resource for research on new treatments and potential vaccines for a respiratory illness that kills about 2 million people each year.

Primate model for metabolic syndrome. Dr. Anthony Commuzie is leading another new project to develop the baboon as a model for metabolic syndrome, which refers to alterations in certain metabolic characteristics that ultimately may give rise to obesity, diabetes and cardiovascular disease.

The chacma baboon as a new genetic resource. In a separate project, Dr. Jeff Rogers leads an initiative to develop chacma baboons as a new genetic resource. The SNPRC already has a one-of-a-kind pedigreed colony of olive baboons, which plays an important role in a wide variety of genetic studies. Dr. Rogers is conducting investigations to identify genetic differences between the two sub-species and determine whether studies with olive baboons, chacma baboons and a hybrid of the two would assist scientists in their hunt for genes that influence the animals' varying degrees of disease susceptibility.

Model for aging research. The SNPRC also has plans to develop a breeding colony of marmoset monkeys as a resource for a variety of potential research projects, including work in neuroscience, biodefense and infectious diseases. The marmoset already is being developed by Dr. Suzette Tardif as an important animal model for aging research. As the smallest monkey species, marmosets also have the shortest lifespan of any primate, considered aged at eight or nine years. This makes the animals ideally suited for studies on the natural processes of aging. Dr. Tardif currently is designing such studies in collaboration with the University of Texas Health Science Center at San Antonio and the University of Texas at San Antonio.

Primate genomics database. Another truly national resource being developed under the leadership of Dr. Michael Mahaney is a primate genomics database. To be created and maintained at SFBR, the database will provide researchers around the country with quick and easy access to comprehensive and up-to-date genomic and genetic information gathered on all species of primates.

SNPRC plays vital role in national research efforts

While the new initiatives funded by the SNPRC base grant renewal will provide future benefit to research programs at SFBR and other institutions, the Southwest National Primate Research Center already serves as a focal point for SFBR's collaborations across the country and around the world. The unique resources and areas of expertise developed through the primate center are critical to the research programs of a broad spectrum of U.S. and international investigators who need to conduct studies with nonhuman primates as they search for new ways to combat disease and improve human health. Without the primate center's resources, many of these research programs would not be possible. Recognizing this, the primate center continually works to enhance and expand its resources with national research needs in

mind, aware that its beneficial impact does and should extend far beyond the Foundation's gates.

In 2004, the SNPRC provided resources and expertise to 144 investigators from 28 states and four foreign countries. These collaborations are helping scientists explore a wide variety of health concerns, including common chronic diseases, developmental abnormalities and infectious diseases. Below are a few examples of national research efforts underway in 2004 that relied on the unique resources of the SNPRC.

Maternal and child health. The baboon is the primate species of choice for research on pregnancy, and with the largest research colony of baboons in the world, the SNPRC provides the critical resource for most of these efforts. In 2004, pregnant baboons from the SNPRC were involved in investigations sponsored by the University of Maryland to study the process of implantation; by Stanford University to perfect fetal cardiac surgery; and by the University of Texas Health Science Center at San Antonio to examine the effects of developmental programming on risks for obesity, diabetes and heart disease.

Infectious diseases. The hepatitis C virus (HCV) is the leading cause of liver failure and liver transplantation in the United States and the primary cause of liver cancer worldwide. No effective vaccine exists, and current treatments, which are difficult on patients, are effective about 50 percent of the time.

To develop improved antiviral strategies, it is necessary for researchers to gain a better understanding of the replication of HCV at a molecular level as well as the factors that determine whether an infection will proceed to chronic infection or viral clearance. Chimpanzees provide a unique resource for these kinds of investigations on

hepatitis C because they are the only animals besides humans that are susceptible to HCV infection. Unlike humans, however, chimpanzees can carry HCV without progressing to liver disease.

The SNPRC maintains one of only four research colonies of chimpanzees in the United States. These animals, as well as the specialized expertise of SFBR and SNPRC staff in managing and working with them, have been critical to the Southeastern Cooperative Hepatitis C Research Group, funded by the National Institutes of Health. This cooperative is composed of three research groups located at the University of Texas Medical Branch at Galveston, Johns Hopkins University and SFBR. In 2004, researchers at SFBR completed their analysis of changes in liver gene expression during chronic HCV infection in the chimpanzee. Through this analysis, they defined 162 genes that were elevated in expression in the liver of a group 10 chimpanzees with chronic HCV infection in comparison to six normal liver baseline samples. Understanding these differences could pave the way toward the development of new therapies.

Brain biology and mental health. The SFBR Genetics Department has a long and illustrious history studying the genetics of cardiovascular, metabolic and infectious diseases. In recent years, the department has also developed research programs in the area of mental health. The SNPRC Genetics Group is developing ties with investigators in the San Antonio area and across the country to research the genetics underlying brain dysfunction and mental disease using primate models. Collaborations in these areas include Dr. Jeff Williams' studies of epilepsy, conducted in collaboration with Dr. Akos Szabo at the University of Texas Health Science Center at San Antonio; Dr. Jeff Rogers' collaborative efforts with Dr. Steve Leigh at the University of Illinois and Dr. Peter Fox at UTHSCSA to study the developing and adult baboon brain through magnetic resonance imaging; and Dr. Rogers' collaboration with Dr. Judy Cameron at the Oregon National Primate Research Center to study the genetics of impulsive and anxious behavior.

Doctoral Staff

(as of December 2004)

Core Scientists

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Raul A. Bastarrachea, M.D.
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Kathleen M. Brasky, V.M.D.
Department of Comparative Medicine

K. Dee Carey, D.V.M., Ph.D.
Chair, Department of Comparative Medicine

Anthony G. Comuzzie, Ph.D.
Department of Genetics

Laura A. Cox, Ph.D.
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Larry B. Cummins, D.V.M.
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SFBR 2004 SCIENTIFIC PUBLICATIONS, GRANTS, CONFERENCES AND SEMINARS

SFBR 2004 SCIENTIFIC PUBLICATIONS

Aida, K., Wang, X. L., Wang, J., Li, C., McDonald, T. J., & Nathanielsz, P. W. (2004). Effect of betamethasone administration to the pregnant baboon at 0.75 gestation on placental eNOS distribution and activity. *Placenta* 25:780-787.

Aida, K., Shi, Q., Wang, J., VandeBerg, J. L., McDonald, T., Nathanielsz, P., & Wang, X. L. (2004). The effects of betamethasone (BM) on endothelial nitric oxide synthase (eNOS) expression in adult baboon femoral arterial endothelial cells. *Journal of Steroid Biochemistry and Molecular Biology* 91:219-224.

Almasy, L. & Blangero, J. (2004). Exploring positional candidate genes: linkage conditional on measured genotype. *Behavior Genetics* 34:173-177.

Almasy, L. (2004). The complex hunt for genes influencing complex disease. *Journal of Thrombosis and Haemostasis* 2:866-867.

Anderson, T. J. (2004). Mapping drug resistance genes in *Plasmodium falciparum* by genome-wide association. *Current Drug Targets - Infectious Disorders* 4:65-78.

Arya, R., Duggirala, R., Jenkinson, C. P., Almasy, L., Blangero, J., O'Connell, P., & Stern, M. P. (2004). Evidence of a novel quantitative-trait locus for obesity on chromosome 4p in Mexican Americans. *American Journal of Human Genetics* 74:272-282.

Avery, C. L., Freedman, B. I., Heiss, G., Kraja, A., Rice, T., Arnett, D., Miller, M. B., Pankow, J. S., Lewis, C. E., Myers, R. H., Hunt, S. C., Almasy, L., & North, K. E. (2004). Linkage analysis of diabetes status among hypertensive families: the Hypertension Genetic Epidemiology Network study. *Diabetes* 53:3307-3312.

Bardi, M., French, J. A., Ramirez, S. M., & Brent, L. (2004). The role of the endocrine system in baboon maternal behavior. *Biological Psychiatry* 55:724-732.

Barrera, A. & Lanford, R. E. (2004). Infection of primary chimpanzee hepatocytes with recombinant hepatitis D virus particles: a surrogate model for hepatitis B virus. *Methods in Molecular Medicine* 96:131-142.

Barrera, A., Guerra, B., Lee, H., & Lanford, R. E. (2004). Analysis of host range phenotypes of primate hepadnaviruses by in vitro infections of hepatitis D virus pseudotypes. *Journal of Virology* 78:5233-5243.

Barrier, B. F., Bates, G. W., Leland, M. M., Leach, D. A., Robinson, R. D., & Propst, A. M. (2004). Efficacy of anti-tumor necrosis factor therapy in the treatment of spontaneous endometriosis in baboons. *Fertility and Sterility* 81 Suppl 1:775-779.

Barrier, B. F., Malinowski, M. J., Dick, E. J., Jr., Hubbard, G. B., & Bates, G. W. (2004). Adenomyosis in the baboon is associated with primary infertility. *Fertility and Sterility* 82 Suppl 3:1091-1094.

Bastarrachea Sosa, R. A. (2004). ¿Cual es el papel actual del tratamiento farmacologico de la obesidad en personas adultas? *Revista De Endocrinologia y Nutricion* 12:S130-S135.

Bastarrachea, R. A., Cole, S. A., & Comuzzie, A. G. (2004). [Genomics of body weight regulation: unraveling the molecular mechanisms predisposing to obesity]. *Medicina Clinica* 123:104-117.

Bastarrachea, R. A., Tejero, E., Cai, G., & Comuzzie, A. G. (2004). Farmacogenomica de la diabesidad: corrigiendo las alteraciones glucolipometabolicas secundarias a un exceso de tejido adiposo. *Revista De Endocrinologia y Nutricion* 12:80-89.

Bastarrachea, R. A., Laviada-Molina, H., & Vasquez-Chavez, C. (2004). Analisis critico de los nuevos criterios que sustentan el diagnostico de pre-diabetes. *Revista De Endocrinologia y Nutricion* 12:90-96.

Continued

Bella, J. N., MacCluer, J. W., Roman, M. J., Almasy, L., North, K. E., Best, L. G., Lee, E. T., Fabsitz, R. R., Howard, B. V., & Devereux, R. B. (2004). Heritability of left ventricular dimensions and mass in American Indians: the Strong Heart Study. *Journal of Hypertension* 22:281-286.

Best, L. G., North, K. E., Tracy, R. P., Lee, E. T., Howard, B. V., Palmieri, V., & MacCluer, J. W. (2004). Genetic determination of acute phase reactant levels: the Strong Heart Study. *Human Heredity* 58:112-116.

Best, L. G., Davidson, M., North, K. E., MacCluer, J. W., Zhang, Y., Lee, E. T., Howard, B. V., DeCroo, S., & Ferrell, R. E. (2004). Prospective analysis of mannose-binding lectin genotypes and coronary artery disease in American Indians: the Strong Heart Study. *Circulation* 109:471-475.

Bethony, J., Williams, J. T., Brooker, S., Gazzinelli, A., Gazzinelli, M. F., LoVerde, P. T., Correa-Oliveira, R., & Kloos, H. (2004). Exposure to *Schistosoma mansoni* infection in a rural area in Brazil. Part III: household aggregation of water-contact behaviour. *Tropical Medicine and International Health* 9:381-389.

Bigger, C. B., Guerra, B., Brasky, K. M., Hubbard, G., Beard, M. R., Luxon, B. A., Lemon, S. M., & Lanford, R. E. (2004). Intrahepatic gene expression during chronic hepatitis C virus infection in chimpanzees. *Journal of Virology* 78:13779-13792.

Bigger, J. E. & Martin, D. W. (2004). Identification of an ICP47 homologue in simian agent 8 (SA8). *Virus Genes* 28:223-225.

Blangero, J. (2004). Localization and identification of human quantitative trait loci: King Harvest has surely come. *Current Opinion in Genetics and Development* 14:233-240.

Brent, L. (2004). Solutions for research chimpanzees. *Lab Animal* 33:37-43.

Brown, L. B., Streeten, E. A., Shuldiner, A. R., Almasy, L. A., Peyser, P. A., & Mitchell, B. D. (2004). Assessment of sex-specific genetic and environmental effects on bone mineral density. *Genetic Epidemiology* 27:153-161.

Brunetti-Pierri, N., Palmer, D. J., Beaudet, A. L., Carey, K. D., Finegold, M., & Ng, P. (2004). Acute toxicity after high-dose systemic injection of helper-dependent adenoviral vectors into non-human primates. *Human Gene Therapy* 15:35-46.

Buil, A., Soria, J. M., Souto, J. C., Almasy, L., Lathrop, M., Blangero, J., & Fontcuberta, J. (2004). Protein C levels are regulated by a quantitative trait locus on chromosome 16: results from the Genetic Analysis of Idiopathic Thrombophilia (GAIT) Project. *Arteriosclerosis, Thrombosis, and Vascular Biology* 24:1321-1325.

Cai, G., Cole, S. A., Freeland-Graves, J. H., MacCluer, J. W., Blangero, J., & Comuzzie, A. G. (2004). Genome-wide scans reveal quantitative trait loci on 8p and 13q related to insulin action and glucose metabolism: the San Antonio Family Heart Study. *Diabetes* 53:1369-1374.

Cai, G., Cole, S. A., Tejero, M. E., Proffitt, J. M., Freeland-Graves, J. H., Blangero, J., & Comuzzie, A. G. (2004). Pleiotropic effects of genes for insulin resistance on adiposity in baboons. *Obesity Research* 12:1766-1772.

Cai, G., Cole, S. A., Bastarrachea-Sosa, R. A., MacCluer, J. W., Blangero, J., & Comuzzie, A. G. (2004). Quantitative trait locus determining dietary macronutrient intakes is located on human chromosome 2p22. *American Journal of Clinical Nutrition* 80:1410-1414.

Cai, G. W., Cole, S. A., Freeland-Graves, J. H., MacCluer, J. W., Blangero, J., & Comuzzie, A. G. (2004). Principal component for metabolic syndrome risk maps to chromosome 4p in Mexican Americans: the San Antonio Family Heart Study. *Human Biology* 76:651-665.

Clarke, J. R., Anderson, T. J., & Bandi, C. (2004). Sexual transmission of a nematode parasite of Wood Mice (*Apodemus sylvaticus*)? *Parasitology* 128:561-568.

Comuzzie, A. G. (2004). Nutrient selection and the genetics of complex phenotypes. *American Journal of Clinical Nutrition* 79:715-716.

Czerwinski, S. A., Mahaney, M. C., Rainwater, D. L., VandeBerg, J. L., MacCluer, J. W., Stern, M. P., & Blangero, J. (2004). Gene × smoking interaction: evidence for effects on low-density lipoprotein size and plasma triglyceride and high-density lipoprotein cholesterol levels. *Human Biology* 76:863-876.

Dieni, S., Inder, T., Yoder, B., Briscoe, T., Camm, E., Egan, G., Denton, D., & Rees, S. (2004). The pattern of cerebral injury in a primate model of preterm birth and neonatal intensive care. *Journal of Neuropathology and Experimental Neurology* 63:1297-1309.

Edenberg, H. J., Dick, D. M., Xuei, X., Tian, H., Almasy, L., Bauer, L. O., Crowe, R. R., Goate, A., Hesselbrock, V., Jones, K., Kwon, J., Li, T. K., Nurnberger, J. I., Jr., O'Connor, S. J., Reich, T., Rice, J., Schuckit, M. A., Porjesz, B., Foroud, T., & Begleiter, H. (2004). Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. *American Journal of Human Genetics* 74:705-714.

Esparza-Gordillo, J., Soria, J. M., Buil, A., Almasy, L., Blangero, J., Fontcuberta, J., & Rodriguez de Cordoba, S. (2004). Genetic and environmental factors influencing the human factor H plasma levels. *Immunogenetics* 56:77-82.

Esparza-Gordillo, J., Soria, J. M., Buil, A., Souto, J. C., Almasy, L., Blangero, J., Rodriguez de Cordoba, S., & Fontcuberta, J. (2004). Genetic correlation between plasma levels of C4BP isoforms containing beta chains and susceptibility to thrombosis. *Journal of Medical Genetics* 41:e5.

Fairbanks, L. A., Newman, T. K., Bailey, J. N., Jorgensen, M. J., Breidenthal, S. E., Ophoff, R. A., Comuzzie, A. G., Martin, L. J., & Rogers, J. (2004). Genetic contributions to social impulsivity and aggressiveness in vervet monkeys. *Biological Psychiatry* 55:642-647.

Finstad, C. L., Wang, C. Y., Kowalski, J., Zhang, M., Li, M. L., Li, X. M., Xia, W. G., Bosland, M. C., Murthy, K. K., Walfield, A. M., Koff, W. C., & Zamb, T. J. (2004). Synthetic luteinizing hormone releasing hormone (LHRH) vaccine for effective androgen deprivation and its application to prostate cancer immunotherapy. *Vaccine* 22:1300-1313.

Fitzpatrick, E., Goring, H. H. H., Liu, H., Borg, A., Forrest, S., Cooper, D. W., Brennecke, S. P., & Moses, E. K. (2004). Fine mapping and SNP analysis of positional candidates at the pre-eclampsia susceptibility locus, PREG1, on chromosome 2. *Human Biology* 76:849-862.

French, J. A., Koban, T., Rukstalis, M., Ramirez, S. M., Bardi, M., & Brent, L. (2004). Excretion of urinary steroids in pre- and postpartum female baboons. *General and Comparative Endocrinology* 137:69-77.

Frost, P. A., Hubbard, G. B., Dammann, M. J., Snider, C. L., Moore, C. M., Hodara, V. L., Giavedoni, L. D., Rohwer, R., Mahaney, M. C., Butler, T. M., Cummins, L. B., McDonald, T. J., Nathanielsz, P. W., & Schlabritz-Loutsevitch, N. E. (2004). White monkey syndrome in infant baboons (*Papio* species). *Journal of Medical Primatology* 33:197-213.

Gautschi, J. T., Amagata, T., Amagata, A., Valeriote, F. A., Mooberry, S. L., & Crews, P. (2004). Expanding the strategies in natural product studies of marine-derived fungi: a chemical investigation of penicillium obtained from deep water sediment. *Journal of Natural Products* 67:362-367.

Giavedoni, L. D., Schlabritz-Loutsevitch, N., Hodara, V. L., Parodi, L. M., Hubbard, G. B., Dudley, D. J., McDonald, T. J., & Nathanielsz, P. W. (2004). Phenotypic changes associated with advancing gestation in maternal and fetal baboon lymphocytes. *Journal of Reproductive Immunology* 64:121-132.

Gorczynski, M. J., Leal, R. M., Mooberry, S. L., Bushweller, J. H., & Brown, M. L. (2004). Synthesis and evaluation of substituted 4-aryloxy- and 4-arylsulfanyl-phenyl-2-aminothiazoles as inhibitors of human breast cancer cell proliferation. *Bioorganic & Medicinal Chemistry* 12:1029-1036.

Havill, L. M., Mahaney, M. C., & Rogers, J. (2004). Genotype-by-sex and environment-by-sex interactions influence variation in serum levels of bone-specific alkaline phosphatase in adult baboons (*Papio hamadryas*). *Bone* 35:198-203.

Havill, L. M. (2004). Osteon remodeling dynamics in *Macaca mulatta*: normal variation with regard to age, sex, and skeletal maturity. *Calcified Tissue International* 74:95-102.

Hlusko, L. J., Suwa, G., Kono, R. T., & Mahaney, M. C. (2004). Genetics and the evolution of primate enamel thickness: A baboon model. *American Journal of Physical Anthropology* 124:223-233.

Continued

Hlusko, L. J., Maas, M. L., & Mahaney, M. C. (2004). Statistical genetics of molar cusp patterning in pedigreed baboons: implications for primate dental development and evolution. *Journal of Experimental Zoology Part B-Molecular and Developmental Evolution* 302B:268-283.

Jeong, S. H., Qiao, M., Nascimbeni, M., Hu, Z., Rehermann, B., Murthy, K., & Liang, T. J. (2004). Immunization with hepatitis C virus-like particles induces humoral and cellular immune responses in nonhuman primates. *Journal of Virology* 78:6995-7003.

Jones, K. A., Porjesz, B., Almasy, L., Bierut, L., Goate, A., Wang, J. C., Dick, D. M., Hinrichs, A., Kwon, J., Rice, J. P., Rohrbaugh, J., Stock, H., Wu, W., Bauer, L. O., Chorlian, D. B., Crowe, R. R., Edenberg, H. J., Foroud, T., Hesselbrock, V., Kuperman, S., Nurnberger, J. J., O'Connor, S. J., Schuckit, M. A., Stimus, A. T., Tischfield, J. A., Reich, T., & Begleiter, H. (2004). Linkage and linkage disequilibrium of evoked EEG oscillations with CHRM2 receptor gene polymorphisms: implications for human brain dynamics and cognition. *International Journal of Psychophysiology* 53:75-90.

Jowett, J. B., Elliott, K. S., Curran, J. E., Hunt, N., Walder, K. R., Collier, G. R., Zimmet, P. Z., & Blangero, J. (2004). Genetic variation in BEACON influences quantitative variation in metabolic syndrome-related phenotypes. *Diabetes* 53:2467-2472.

Kaba, N. K., Francis, C. W., Moss, A. J., Zareba, W., Oakes, D., Knox, K. L., Fernandez, I. D., & Rainwater, D. L. (2004). Effects of lipids and lipid-lowering therapy on hemostatic factors in patients with myocardial infarction. *Journal of Thrombosis and Haemostasis* 2:718-725.

Kammerer, C. M., Dualan, A. A., Samollow, P. B., Perisse, A. R., Bauer, R. L., MacCluer, J. W., O'Leary, D. H., & Mitchell, B. D. (2004). Bone mineral density, carotid artery intimal medial thickness, and the vitamin D receptor BsmI polymorphism in Mexican American women. *Calcified Tissue International* 75:292-298.

Kammerer, C. M., Gouin, N., Samollow, P. B., VandeBerg, J. F., Hixson, J. E., Cole, S. A., MacCluer, J. W., & Atwood, L. D. (2004). Two quantitative trait loci affect ACE activities in Mexican-Americans. *Hypertension* 43:466-470.

Kent, J. W., Jr., Comuzzie, A. G., Mahaney, M. C., Almasy, L., Rainwater, D. L., VandeBerg, J. L., MacCluer, J. W., & Blangero, J. (2004). Intercellular adhesion molecule-1 concentration is genetically correlated with insulin resistance, obesity, and HDL concentration in Mexican Americans. *Diabetes* 53:2691-2695.

Kimata, J. T., Wilson, J. M., & Patel, P. G. (2004). The increased replicative capacity of a late-stage simian immunodeficiency virus mne variant is evident in macrophage- or dendritic cell-T-cell cocultures. *Virology* 327:307-317.

Kushwaha, R. S., VandeBerg, J. F., & VandeBerg, J. L. (2004). Effect of dietary cholesterol with or without saturated fat on plasma lipoprotein cholesterol levels in the laboratory opossum (*Monodelphis domestica*) model for diet-induced hyperlipidaemia. *British Journal of Nutrition* 92:63-70.

Kushwaha, R. S., McGill Jr., H. C., & Hausheer, F. H. (2004). Effect of synthetic truncated apolipoprotein C-I peptide on plasma lipoprotein cholesterol in nonhuman primates. *Journal of Biomedicine & Biotechnology* 2004:177-184.

Kushwaha, R. S., VandeBerg, J. F., Rodriguez, R., & VandeBerg, J. L. (2004). Cholesterol absorption and hepatic acyl-coenzyme A: cholesterol acyltransferase activity play major roles in lipemic response to dietary cholesterol and fat in laboratory opossums. *Metabolism* 53:817-822.

Lanford, R. E., Guerra, B., Chavez, D., Bigger, C., Brasky, K. M., Wang, X. H., Ray, S. C., & Thomas, D. L. (2004). Cross-genotype immunity to hepatitis C virus. *Journal of Virology* 78:1575-1581.

Lange, J. H. (2004). Airborne mold clearance criteria for remediation. *Annals of Allergy, Asthma & Immunology* 92:480-481.

Lee, S. J., Garza, L., Yao, J., Notkins, A. L., & Zhou, P. (2004). A nonneutralizing anti-HIV-1 antibody turns into a neutralizing antibody when expressed on the surface of HIV-1-susceptible cells: a new way to fight HIV. *Journal of Immunology* 173:4618-4626.

Lott, L., Notvall, L., & Lanford, R. E. (2004). Expression and purification of functional hepatitis B virus polymerase in the baculovirus insect cell system. *Methods in Molecular Medicine* 95:271-279.

Marks, D. L., Boucher, N., Lanouette, C. M., Perusse, L., Brookhart, G., Comuzzie, A. G., Chagnon, Y. C., & Cone, R. D. (2004). Ala67Thr polymorphism in the Agouti-related peptide gene is associated with inherited leanness in humans. *American Journal of Medical Genetics. Part A* 126:267-271.

Martin, L. J., Comuzzie, A. G., Sonnenberg, G. E., Myklebust, J., James, R., Marks, J., Blangero, J., & Kissebah, A. H. (2004). Major quantitative trait locus for resting heart rate maps to a region on chromosome 4. *Hypertension* 43:1146-1151.

Martin, L. J., Cianflone, K., Zakarian, R., Nagrani, G., Almasy, L., Rainwater, D. L., Cole, S., Hixson, J. E., MacCluer, J. W., Blangero, J., & Comuzzie, A. G. (2004). Bivariate linkage between acylation-stimulating protein and BMI and high-density lipoproteins. *Obesity Research* 12:669-678.

Mooberry, S. L., Randall-Hlubek, D. A., Leal, R. M., Hegde, S. G., Hubbard, R. D., Zhang, L., & Wender, P. A. (2004). Microtubule-stabilizing agents based on designed laulimalide analogues. *Proceedings of the National Academy of Sciences of the United States of America* 101:8803-8808.

Nakao, Y., Yoshida, W. Y., Takada, Y., Kimura, J., Yang, L., Mooberry, S. L., & Scheuer, P. J. (2004). Kulokekahilide-2, a cytotoxic depsipeptide from a cephalaspidean mollusk *Philinopsis speciosa*. *Journal of Natural Products* 67:1332-1340.

Nevill, C. H., Friend, T. H., & Toscano, M. J. (2004). Survey of transport environments of circus tigers (*Panthera tigris*). *Journal of Zoo and Wildlife Medicine* 35:167-174.

Newman, T. K., Jolly, C. J., & Rogers, J. (2004). Mitochondrial phylogeny and systematics of baboons (*Papio*). *American Journal of Physical Anthropology* 124:17-27.

North, K. E., Rose, K. M., Borecki, I. B., Oberman, A., Hunt, S. C., Miller, M. B., Blangero, J., Almasy, L., & Pankow, J. S. (2004). Evidence for a gene on chromosome 13 influencing postural systolic blood pressure change and body mass index. *Hypertension* 43:780-784.

Patterson, J. L. (2004). SARS: from identification to vaccination. *Contagion* 1:12-15.

Porter, B. F., Goens, S. D., Brasky, K. M., & Hubbard, G. B. (2004). A case report of hepatocellular carcinoma and focal nodular hyperplasia with a myelolipoma in two chimpanzees and a review of spontaneous hepatobiliary tumors in non-human primates. *Journal of Medical Primatology* 33:38-47.

Porter, B. F., Summers, B. A., Leland, M. M., & Hubbard, G. B. (2004). Glioblastoma multiforme in three baboons (*Papio* spp.). *Veterinary Pathology* 41:424-428.

Rainwater, D. L., Mahaney, M. C., VandeBerg, J. L., Brush, G., Almasy, L., Blangero, J., Dyke, B., Hixson, J. E., Cole, S. A., & MacCluer, J. W. (2004). A quantitative trait locus influences coordinated variation in measures of ApoB-containing lipoproteins. *Atherosclerosis* 176:379-386.

Rainwater, D. L., Moore, P. H., Jr., & Gamboa, I. O. (2004). Improved method for making nondenaturing composite gradient gels for the electrophoretic separation of lipoproteins. *Journal of Lipid Research* 45:773-775.

Ramirez, S. M., Bardi, M., French, J. A., & Brent, L. (2004). Hormonal correlates of changes in interest in unrelated infants across the peripartum period in female baboons (*Papio hamadryas anubis* sp.). *Hormones and Behavior* 46:520-528.

Ro, Y. T., Kim, E. J., Lee, H. I., Saiz, M., Carrion, R., Jr., & Patterson, J. L. (2004). Evidence that the fully assembled capsid of *Leishmania* RNA virus 1-4 possesses catalytically active endoribonuclease activity. *Experimental and Molecular Medicine* 36:145-156.

Continued

Rogers, J., Martin, L. J., Comuzzie, A. G., Mann, J. J., Manuck, S. B., Leland, M., & Kaplan, J. R. (2004). Genetics of monoamine metabolites in baboons: overlapping sets of genes influence levels of 5-hydroxyindolacetic acid, 3-hydroxy-4-methoxyphenylglycol, and homovanillic acid. *Biological Psychiatry* 55:739-744.

Roper, C., Pearce, R., Nair, S., Sharp, B., Pearce, R., Nair, S., Sharp, B., Nosten, F., & Anderson, T. (2004). Stopping the spread of drug-resistant malaria - Response. *Science* 306:2040c.

Roper, C., Pearce, R., Nair, S., Sharp, B., Nosten, F., & Anderson, T. (2004). Intercontinental spread of pyrimethamine-resistant malaria. *Science* 305:1124.

Samollow, P. B., Kammerer, C. M., Mahaney, S. M., Schneider, J. L., Westenberger, S. J., VandeBerg, J. L., & Robinson, E. S. (2004). First-generation linkage map of the gray, short-tailed opossum, *Monodelphis domestica*, reveals genome-wide reduction in female recombination rates. *Genetics* 166:307-329.

Samollow, P. B., Perez, G., Kammerer, C. M., Finegold, D., Zwartjes, P. W., Havill, L. M., Comuzzie, A. G., Mahaney, M. C., Goring, H. H., Blangero, J., Foley, T. P., & Barmada, M. M. (2004). Genetic and environmental influences on thyroid hormone variation in Mexican Americans. *Journal of Clinical Endocrinology and Metabolism* 89:3276-3284.

Schlabritz-Loutsevitch, N. E., Hubbard, G. B., Dammann, M. J., Jenkins, S. L., Frost, P. A., McDonald, T. J., & Nathanielsz, P. W. (2004). Normal concentrations of essential and toxic elements in pregnant baboons and fetuses (*Papio* species). *Journal of Medical Primatology* 33:152-162.

Schlabritz-Loutsevitch, N. E., Hubbard, G. B., Frost, P. A., Cummins, L. B., Dick, E. J., Jr., Nathanielsz, P. W., & McDonald, T. J. (2004). Abdominal pregnancy in a baboon: a first case report. *Journal of Medical Primatology* 33:55-59.

Schlabritz-Loutsevitch, N. E., Howell, K., Rice, K., Glover, E. J., Nevill, C. H., Jenkins, S. L., Bill, C. L., Frost, P. A., McDonald, T. J., & Nathanielsz, P. W. (2004). Development of a system for individual feeding of baboons maintained in an outdoor group social environment. *Journal of Medical Primatology* 33:117-126.

Shen, Y. H., Utama, B., Wang, J., Raveendran, M., Senthil, D., Waldman, W. J., Belcher, J. D., Vercellotti, G., Martin, D., Mitchelle, B. M., & Wang, X. L. (2004). Human cytomegalovirus causes endothelial injury through the ataxia telangiectasia mutant and p53 DNA damage signaling pathways. *Circulation Research* 94:1310-1317.

Shi, Q., Wang, J., Wang, X. L., & VandeBerg, J. L. (2004). Comparative analysis of vascular endothelial cell activation by TNF-alpha and LPS in humans and baboons. *Cell Biochemistry and Biophysics* 40:289-304.

Shi, Q., Aida, K., VandeBerg, J. L., & Wang, X. L. (2004). Passage-dependent changes in baboon endothelial cells—relevance to *in vitro* aging. *DNA and Cell Biology* 23:502-509.

Shin, S. D., Suh, G. J., Rhee, J. E., Sung, J., & Kim, J. (2004). Epidemiologic characteristics of death by poisoning in 1991-2001 in Korea. *Journal of Korean Medical Science* 19:186-194.

Shin, S. D., Suh, G. J., Sung, J., & Kim, J. (2004). Epidemiologic characteristics of death by burn injury from 1991 to 2001 in Korea. *Burns* 30:820-828.

Smucny, D. A., Abbott, D. H., Mansfield, K. G., Schultz-Darken, N. J., Yamamoto, M. E., Alencar, A. I., & Tardif, S. D. (2004). Reproductive output, maternal age, and survivorship in captive common marmoset females (*Callithrix jacchus*). *American Journal of Primatology* 64:107-121.

Smucny, D. A., Allison, D. B., Ingram, D. K., Roth, G. S., Kemnitz, J. W., Kohama, S. G., Lane, M. A., & Black, A. (2004). Update [to]: Changes in blood chemistry and hematology variables during aging in captive rhesus macaques (*Macaca mulatta*). J Med Primatol 30:161-173, 2001. *Journal of Medical Primatology* 33:48-54.

Song, Y. M., Sung, J., Davey, S. G., & Ebrahim, S. (2004). Body mass index and ischemic and hemorrhagic stroke: a prospective study in Korean men. *Stroke* 35:831-836.

Sonnenberg, G. E., Krakower, G. R., Martin, L. J., Olivier, M., Kwitek, A. E., Comuzzie, A. G., Blangero, J., & Kissebah, A. H. (2004). Genetic determinants of obesity-related lipid traits. *Journal of Lipid Research* 45:610-615.

Sonnenschein, R. N., Farias, J. J., Tenney, K., Mooberry, S. L., Lobkovsky, E., Clardy, J., & Crews, P. (2004). A further study of the cytotoxic constituents of a milnamide-producing sponge. *Organic Letters* 6:779-782.

Steppan, S., Adkins, R., & Anderson, J. (2004). Phylogeny and divergence-date estimates of rapid radiations in muroid rodents based on multiple nuclear genes. *Systematic Biology* 53:533-553.

Subedi, S., Tausig, M., Subedi, J., Broughton, C. L., & Williams-Blangero, S. (2004). Mental illness and disability among elders in developing countries: the case of Nepal. *Journal of Aging and Health* 16:71-87.

Szabo, C. A., Leland, M. M., Sztonak, L., Restrepo, S., Haines, R., Mahaney, M. A., & Williams, J. T. (2004). Scalp EEG for the diagnosis of epilepsy and photosensitivity in the baboon. *American Journal of Primatology* 62:95-106.

Tardif, S., Power, M., Layne, D., Smucny, D., & Ziegler, T. (2004). Energy restriction initiated at different gestational ages has varying effects on maternal weight gain and pregnancy outcome in common marmoset monkeys (*Callithrix jacchus*). *British Journal of Nutrition* 92:841-849.

Tardif, S. D. & Bales, K. L. (2004). Relations among birth condition, maternal condition, and postnatal growth in captive common marmoset monkeys (*Callithrix jacchus*). *American Journal of Primatology* 62:83-94.

Tejero, M. E., Proffitt, J. M., Cole, S. A., Freeland-Graves, J. H., Cai, G., Peebles, K. W., Cox, L. A., Mahaney, M. C., Rogers, J., VandeBerg, J. L., Blangero, J., & Comuzzie, A. G. (2004). Quantitative genetic analysis of glucose transporter 4 mRNA levels in baboon adipose. *Obesity Research* 12:1652-1657.

Tejero, M. E., Freeland-Graves, J. H., Proffitt, J. M., Peebles, K. W., Cai, G., Cole, S. A., & Comuzzie, A. G. (2004). Adiponectin but not resistin is associated with insulin resistance-related phenotypes in baboons. *Obesity Research* 12:871-877.

Thomson, M. A., Yoder, B. A., Winter, V. T., Martin, H., Catland, D., Siler-Khodr, T. M., & Coalson, J. J. (2004). Treatment of immature baboons for 28 days with early nasal continuous positive airway pressure. *American Journal of Respiratory Critical Care Medicine* 169:1054-1062.

van den Broek, I. V., van der Wardt, S., Talukder, L., Chakma, S., Brockman, A., Nair, S., & Anderson, T. C. (2004). Drug resistance in *Plasmodium falciparum* from the Chittagong Hill Tracts, Bangladesh. *Tropical Medicine and International Health* 9:680-687.

VandeBerg, J. L. (2004). Need for primate models in biomedical research. *Gynecologic and Obstetric Investigation* 57:6-8.

Vilozny, B., Amagata, T., Mooberry, S. L., & Crews, P. (2004). A new dimension to the biosynthetic products isolated from the sponge *Negombata magnifica*. *Journal of Natural Products* 67:1055-1057.

Wang, Q. F., Liu, X., O'Connell, J., Peng, Z., Krauss, R. M., Rainwater, D. L., VandeBerg, J. L., Rubin, E. M., Cheng, J. F., & Pennacchio, L. A. (2004). Haplotypes in the APOA1-C3-A4-A5 gene cluster affect plasma lipids in both humans and baboons. *Human Molecular Genetics* 13:1049-1056.

Wang, X. L., Wang, J., Shi, Q., Dee, C. K., & VandeBerg, J. L. (2004). Arterial wall-determined risk factors to vascular diseases: a nonhuman primate model. *Cell Biochemistry and Biophysics* 40:371-388.

Wang, X. L., Rainwater, D. L., Leone, A., & Mahaney, M. C. (2004). Effects of diabetes on plasma nitrotyrosine levels. *Diabetic Medicine* 21:577-580.

Continued

Wang, X. L., Rainwater, D. L., Mahaney, M. C., & Stocker, R. (2004). Cosupplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. *American Journal of Clinical Nutrition* 80:649-655.

Wang, Z., Dooley, T. P., Curto, E. V., Davis, R. L., & VandeBerg, J. L. (2004). Cross-species application of cDNA microarrays to profile gene expression using UV-induced melanoma in *Monodelphis domestica* as the model system. *Genomics* 83:588-599.

Wang, Z. & VandeBerg, J. L. (2004). Cloning and molecular characterization of a human ortholog of *Monodelphis* TRAPD in ultraviolet B-induced melanoma. *Melanoma Research* 14:107-114.

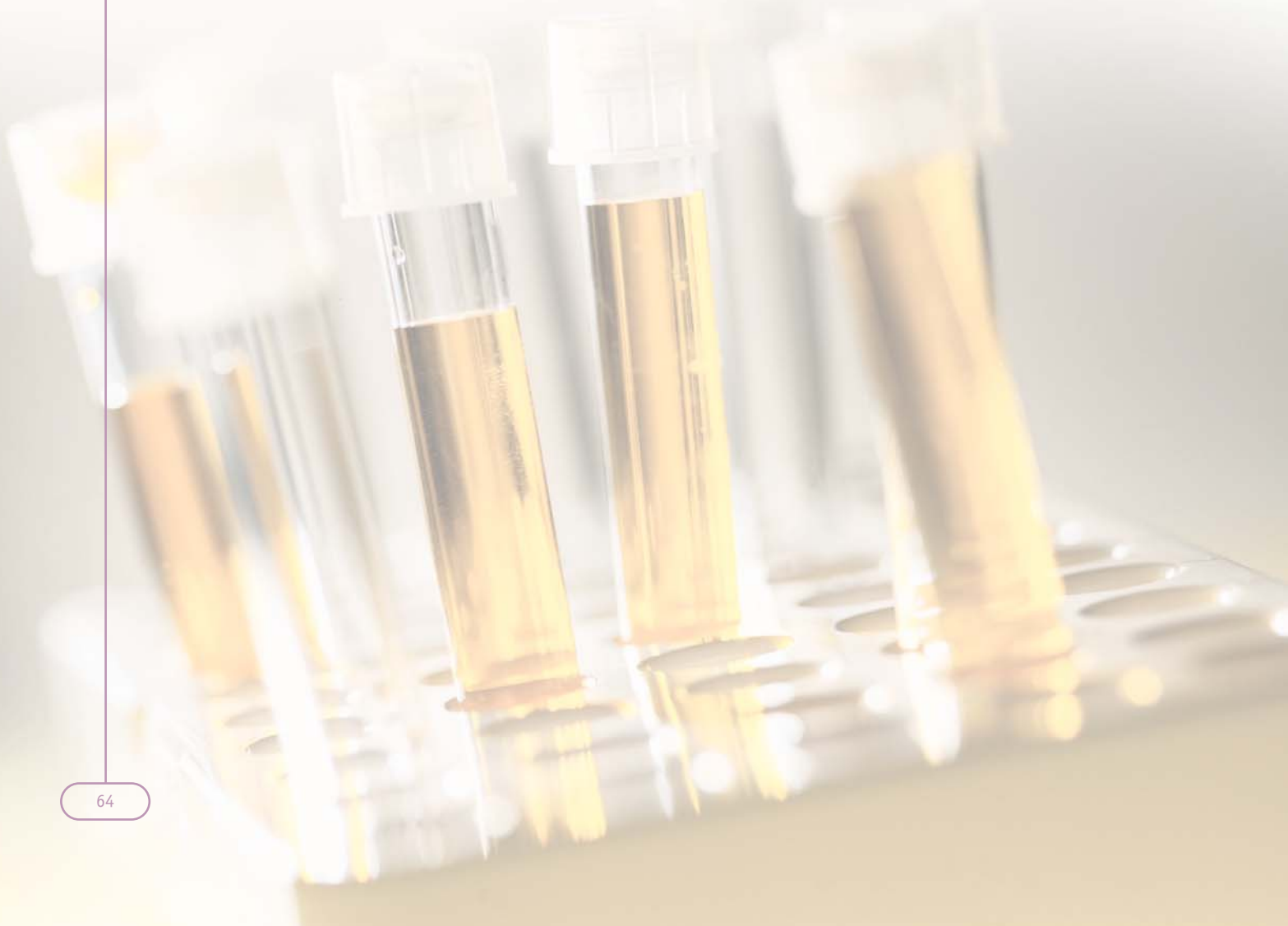
Williams, J. T. & Blangero, J. (2004). Power of variance component linkage analysis-II. Discrete traits. *Annals of Human Genetics* 68:620-632.

Williams-Blangero, S. (2004). The human genome project and advances in anthropological genetics. *Human Biology* 76:801-804.

Williams-Blangero, S., Correa-Oliveira, R., VandeBerg, J. L., Subedi, J., Upadhayay, R. P., Rai, D. R., Jha, B., & Blangero, J. (2004). Genetic influences on plasma cytokine variation in a parasitized population. *Human Biology* 76:515-525.

Winchester, R., Pitt, J., Charurat, M., Magder, L. S., Goring, H. H., Landay, A., Read, J. S., Shearer, W., Handelsman, E., Luzuriaga, K., Hillyer, G. V., & Blattner, W. (2004). Mother-to-child transmission of HIV-1: strong association with certain maternal HLA-B alleles independent of viral load implicates innate immune mechanisms. *Journal of Acquired Immune Deficiency Syndromes* 36:659-670.

Zabalgoitia, M., Ventura, J., Lozano, J. L., Anderson, L., Carey, K. D., Hubbard, G. B., Williams, J. T., & VandeBerg, J. L. (2004). Myocardial contrast echocardiography in assessing microcirculation in baboons with Chagas disease. *Microcirculation* 11:271-278.



ADVANCING SCIENCE THROUGH EDUCATION:

SFBR-sponsored programs benefit local, national, and international researchers

Conferences and workshops hosted in 2004

Genetic Analysis Workshop 14

Date: September 7-10, 2004
Location: Noordwijkerhout, Holland

Initiated in 1982 by Jean W. MacCluer, Ph.D., senior scientist in the SFBR Department of Genetics, the Genetic Analysis Workshops are a collaborative effort among genetic epidemiologists to evaluate and compare statistical genetic methods. For each GAW, topics are chosen that are relevant to current analytical problems in genetic epidemiology, and sets of real or computer-simulated data are distributed to investigators worldwide. Results of analyses are discussed and compared at meetings held in even-numbered years, and the workshop proceedings are published in the journal *Genetic Epidemiology* as well as on the Web. Dr. MacCluer continues to chair the GAW Advisory Committee, which includes fellow SFBR geneticist Laura Almasy, Ph.D., who is an important contributor to the workshop's organization, as well as other distinguished scientists from the United States and Europe.

22nd Annual Symposium on Nonhuman Primate Models for AIDS

Date: November 3-6, 2004
Location: Westin Riverwalk Hotel, San Antonio, Texas

This symposium, which rotates annually among the eight National Primate Research Centers and their respective cities, is considered the premier forum for the presentation and exchange of the most recent scientific

advances in AIDS research utilizing the nonhuman primate model. Each year, the event draws nearly 250 researchers from across the United States and overseas. This year's event was held in San Antonio and hosted by the Southwest National Primate Research Center (SNPRC). Luis Giavedoni, Ph.D., associate scientist in the SFBR Department of Virology and Immunology and a core scientist with the SNPRC, chaired the organizing committee for this international event, which drew participants from the United States, Japan, China, Germany, France, England, Australia and Italy. During five scientific sessions with 50 oral presentations, along with 92 poster presentations, leading scientists presented their latest findings in primate pathogenesis, immunology, genomics, virology, vaccines and therapeutics. The symposium was supported in part by grants from the National Center for Research Resources, National Institute for Allergy and Infectious Diseases, Office of AIDS Research, and National Cancer Institute, National Institutes of Health. Event planners and organizers included numerous members of SFBR and SNPRC faculty and staff. The organizing committee included Luis Giavedoni, Ph.D., chair; Suzette Tardif, Ph.D., co-chair; and members Barbara Gault, Silvia Geedman and April Hopstetter. The scientific program committee included Dr. Giavedoni as chair along with members Jonathan Allan, D.V.M.; Krishna Murthy, D.V.M., Ph.D.; Jeffrey Rogers, Ph.D.; and Paul Zhou, Ph.D., along with national members from other primate centers and affiliated research institutions, as well as from the National Institutes of Health.

Anthropological and Primate Genetics Workshop

Date: November 18-20, 2004
Location: Southwest Foundation for Biomedical Research, San Antonio, Texas

The American Association of Anthropological Genetics and the Southwest Foundation for Biomedical Research teamed up to sponsor this workshop, which focused on the study of normal variation and genetic epidemiology in both human and nonhuman primates. Presenters introduced concepts, methods, and results of genetic analysis with the aim of helping participants design their own genetic studies. The workshop was intended for graduate students and faculty interested in integrating various genetic methods into their research programs, but it also was open to advanced undergraduates and others with a serious interest in these types of analyses. The workshop ended with a special question-and-answer session with a panel of researchers who could answer participants' specific questions regarding data collection, the potential of previously collected data, opportunities for training and collaboration, and other topics. Lorena Havill, Ph.D., staff scientist in the Department of Genetics, chaired this informative and well-attended event with the help of Deidre Winnier, Ph.D., a postdoctoral scientist with the department. The workshop was made possible through the generous sponsorship of several organizations: Applied Biosystems; M&A Technology; Purina Mills, Inc.; Sigma Solutions; and VWR International, Inc.

SFBR FACULTY SEMINAR SERIES

Throughout the year, the Southwest Foundation for Biomedical Research hosts a series of seminars featuring scientific experts from its own faculty as well as other top researchers from across the United States, who present information about their latest efforts and findings in the search for new ways to fight diseases of every kind. SFBR makes this seminar series open to the public to help meet the continuing education needs of scientists at its peer research institutions throughout the local community. A note of thanks goes to Tim Anderson, Ph.D., assistant scientist in the Department of Genetics, who organized the following programs in 2004.

White Monkey Syndrome: Is the Problem Solved?

May 6, 2004
Presented by Natalia Schlabritz-Loutsevitch, M.D., Ph.D.
Assistant Professor
Department of Obstetrics and Gynecology
New York University School of Medicine
(Dr. Schlabritz-Loutsevitch, who also is an adjunct scientist in the Department of Comparative Medicine at SFBR, has recently joined the University of Texas Health Science Center at San Antonio as an assistant professor in the Department of Obstetrics and Gynecology.)

Famous Animal Experiments: A Historical Perspective

May 21, 2004
Presented by William Stone, Ph.D.
Interim Scientific Director
Southwest Foundation for Biomedical Research

Fetal and Placental Adaptation to Maternal Under-Nutrition: The Baboon Model

June 24, 2004
Presented by Peter W. Nathanielsz, M.D., Ph.D., Sc.D.
Director, Center for Women's Health Research
Professor of Obstetrics and Gynecology
New York University School of Medicine
(Dr. Nathanielsz, who also is an adjunct scientist at SFBR, has recently joined the faculty at the University of Texas Health Science Center at San Antonio.)

Preclinical Pharmacology of GHB: Drug of Abuse or a New Class of Therapeutics?

July 15, 2004
Presented by Charles P. France, Ph.D.
Professor, Department of Pharmacology
The University of Texas Health Science Center at San Antonio

Sex and Paternal Age Effects on the Human Mutation Rate: Still a Puzzle

July 29, 2004
Presented by James F. Crow, Ph.D.
Emeritus Professor of Genetics & Medical Genetics
Laboratory of Genetics
University of Wisconsin-Madison

Activity Budgets and Gastrointestinal Physiology in Grey Bamboo Lemurs

August 19, 2004
Presented by Christina Grassi, Ph.D.
Staff Scientist and Director of Behavior and Enrichment
Department of Comparative Medicine
Southwest Foundation for Biomedical Research

The Monodelphis Model for Cancer Research

September 23, 2004
Presented by Zhiqiang Wang, Ph.D.
Staff Scientist, Department of Genetics
Southwest Foundation for Biomedical Research

Polyunsaturated Fatty Acid Nutrition for Neural Development in Neonatal Baboons

December 9, 2004
Presented by J. Thomas Brenna, Ph.D.
Professor, Division of Nutritional Sciences
Cornell University, Ithaca, New York

NEW GRANTS AND CONTRACTS AWARDED IN 2004

FEDERAL RESEARCH GRANTS AND CONTRACTS

	Length of Grant	Total Amount to SFBR
NIH *Southwest National Primate Research Center* Dr. Frank Ledford Jr., principal investigator Dr. John VandeBerg, director	5 years	$27,899,701
NIH *Collaborative Program in BPD* Dr. Jacqueline Coalson, University of Texas Health Science Center at San Antonio, principal investigator; Dr. K. Dee Carey, SFBR, veterinary services director	5 years	$ 8,704,478
NIH *Rhesus Breeding Colony in Nepal and Importation to U.S.A.* Dr. John VandeBerg, principal investigator	5 years	$ 3,485,440
NIH *Baboon Model for the Study of Primate Maternal Behavior* Dr. Linda Brent, principal investigator	5 years	$ 1,912,099
NIH *Cholesterol Responsive Genes in the Laboratory Opossum* Dr. John VandeBerg, principal investigator	5 years	$ 1,756,772
NIH *GBV-B: A Small Primate Model for Hepatitis C Infection* Dr. Robert Lanford, principal investigator	5 years	$ 1,675,000
NIH *Genetics of Kidney Disease in Zuni Indians* Dr. Philip Zager, University of New Mexico Health Science Center, principal investigator; Dr. Jean MacCluer, SFBR, co-principal investigator	4 years	$ 1,488,599
NIH *Baboon Model for Genetics of Human Generalized Epilepsy* Dr. Jeff Williams, principal investigator	4 years	$ 1,153,475
NIH *Region VI Center for Biodefense and Emerging Infections: Small Animal Core* Dr. Rick Lyons, University of New Mexico Health Science Center, principal investigator; Dr. Jean Patterson, SFBR, core leader	4 years	$ 838,849

	Length of Grant	Total Amount to SFBR
NIH *Southwest National Primate Research Center – supplement* Dr. Frank Ledford Jr., principal investigator Dr. John VandeBerg, director	1 year	$ 531,930
NIH *Mapping Genes for Neurocognitive Endophenotypes* Dr. Susan Santangelo, Massachusetts General Hospital, principal investigator; Dr. Sarah Williams-Blangero, SFBR, co-principal investigator	5 years	$ 402,458
NIH *Southwest National Primate Research Center – supplement* Dr. Frank Ledford Jr., principal investigator Dr. John VandeBerg, director	1 year	$ 376,000
NIH *Collaborative Study on the Genetics of Alcoholism* Dr. Henri Begleiter, State University of New York, principal investigator Dr. Laura Almasy, SFBR, co-principal investigator	5 years	$ 368,506
NIH *Gene Expression Analyses During IFN Antiviral Therapy* Dr. Robert Lanford, principal investigator	2 years	$ 335,000
NIH *Diabesity Gene Discovery at Chromosome 6q23* Dr. Christopher Jenkinson, University of Texas Health Science Center at San Antonio, principal investigator; Dr. Ravindranath Duggirala, SFBR, co-investigator	5 years	$ 303,064
NIH *IgE Peptide Vaccine for Immunotherapy of Allergy* Dr. Change Yi Wang, United Biomedical, Inc., principal investigator Dr. Krishna Murthy, SFBR, co-investigator	1 year	$ 248,813
USAMRIID *Sale and Per Diem of Macaques* Dr. K. Dee Carey, project manager	6 months	$ 229,779
NIH *Genetics of Bone Structural Geometry: Framingham Cohorts* Dr. David Karasik, Hebrew Rehabilitation Center for Aged, principal investigator Dr. Michael Mahaney, SFBR, co-principal investigator	3 years	$ 179,171
NIH *Mopeia/Lassa Chimeric Vaccine Against Lassa Fever* Dr. Igor Lukashevic, University of Maryland, principal investigator Dr. Jean Patterson, SFBR, co-principal investigator	1 year	$ 153,001
NIH *Genetic Linkage Mapping in Rhesus Monkeys – supplement* Dr. Jeffrey Rogers, principal investigator	5 months	$ 124,754
NIH *Southwest National Primate Research Center – supplement* Dr. Frank Ledford Jr., principal investigator Dr. John VandeBerg, director	1 year	$ 108,044

Continued

	Length of Grant	Total Amount to SFBR
NIH *Association Analysis of SNPs in Longevity Assurance Genes* Dr. Yousin Suh, University of Texas Health Science Center at San Antonio, principal investigator; Dr. Ravindranath Duggirala, SFBR, co-principal investigator	5 years	$ 106,114
FBI *Bacillus Microscale Proteomics* Dr. Richard Drake, Eastern Virginia Medical School, principal investigator Dr. Jean Patterson, SFBR, co-principal investigator	1 year	$ 105,542
NIH *Glucocorticoid Programming-Pituitary Adrenal Axis – Phase II – supplement* Dr. Peter Nathanielsz, New York University, principal investigator Dr. Larry B. Cummins, project manager	1 year	$ 104,533
Miscellaneous federal grants and contracts (under $100,000 each)		$ 805,198
Total Federal Research Grants and Contracts		**$53,396,320**

COMMERCIAL RESEARCH CONTRACTS

Department of Comparative Medicine (23)		$1,708,755
Department of Virology and Immunology (12)		$ 672,191
Department of Genetics (4)		$ 654,425
Department of Organic Chemistry (2)		$ 84,101
Total Commercial Research Contracts		**$ 3,119,472**

RESEARCH GRANTS FROM PHILANTHROPIC DONORS

Mathers Charitable Foundation *Neuroscience Center for Ingestive Behavior* Dr. Robert Shade, principal investigator	3 years	$1,050,000
Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation *Monodelphis Colony Support* Dr. John VandeBerg, principal investigator	1 year	$ 366,000
W.B. and E.G. Stuart Trust *Cancer Drug Development* Dr. Susan Mooberry, principal investigator	1 year	$ 50,000

	Length of Grant	Total Amount to SFBR
The Ellison Medical Foundation *Dengue Virus Pathogenesis in Reconstituted SCID Mice* Dr. Rebeca Rico-Hesse, principal investigator	1 year	$ 50,000
Amon G. Carter Foundation *Cancer Drug Discovery Program* Dr. Susan Mooberry, principal investigator	1 year	$ 50,000
Morrison Trust *Antiangiogenic Activities of the Laulimalides* Dr. Susan Mooberry, principal investigator	1 year	$ 47,040
Joe and Jesse Crump Foundation *Cancer Drug Development* Dr. Susan Mooberry, principal investigator	1 year	$ 30,000
San Antonio Area Foundation from the Semp Russ Foundation *Diagnostic Antibodies for SARS* Dr. Andrew Hayhurst, principal investigator	1 year	$ 30,000
Southwest Foundation Forum *A Novel Approach to Deliver Therapeutic Human Antibodies Specific for Emerging Viruses* Dr. Andrew Hayhurst, principal investigator	1 year	$ 25,000
Southwest Foundation Forum *Genetic Variation of Resistin and Insulin Resistance in Baboons* Dr. M. Elizabeth Tejero, principal investigator	1 year	$ 24,872
Southwest Foundation Forum *Genetics of Osteon Remodeling in the Baboon* Dr. Lorena Havill, principal investigator	1 year	$ 22,492
Shelby Rae Tengg Foundation *Identification of New Taccalonolides – supplement* Dr. Susan Mooberry, principal investigator	1 year	$ 21,253
Raymond Dickson Foundation *Library Electronic Classroom*	1 year	$ 20,000
Southwest Foundation Forum *Search for Genes Influencing Age-Related Blood Pressure Variation in Mexican Americans* Dr. Guowen Cai, principal investigator	1 year	$ 19,080
Rowan Scientific Fund *Bridge Funding for Marmoset Colony and Research* Dr. Suzette Tardif, principal investigator	1 year	$ 18,539
Susan Freeborn Kerr Foundation *Isolate Sufficient Quantities of New Taccalonolide to Determine Effectiveness Against Human Cancers* Dr. Susan Mooberry, principal investigator	1 year	$ 17,000
Jane Cheever Powell *Obesity Research* Dr. Anthony Comuzzie, principal investigator	1 year	$ 6,000

Continued

	Length of Grant	Total Amount to SFBR
Peter and Beth Dahlberg *Cardiovascular Research – supplement* Dr. Henry C. McGill Jr., principal investigator	16 months	$ 1,000
Total Philanthropic Grants[i]		**$ 1,848,276**
TOTAL OF NEW GRANTS AND CONTRACTS AWARDED DURING 2004		**$58,364,068**

i *The following philanthropic grants were made as gifts to SFBR in previous years, but the funds were awarded in 2004 for the recruitment of Dr. Eric Moses and the initial funding of his laboratory for research on the genetics of preeclampsia.*

	Length of Grant	Total Amount to SFBR
Elizabeth Huth Coates Charitable Foundation *Scientific Recruiting* For the Recruitment of Dr. Eric Moses	3 years	$ 500,000
Irene Wischer *Scientific Recruiting* For the recruitment of Dr. Eric Moses	3 years	$ 73,543

MISSION, VISION, VALUES

THE MISSION of Southwest Foundation for Biomedical Research is to conduct fundamental and applied research for the betterment of humanity. In carrying out this mission, Southwest Foundation seeks to develop cost-effective strategies for the prevention and treatment of disease.

Southwest Foundation, its scientists and its staff are dedicated to the principles of free and objective inquiry. Scientists are encouraged to pursue research of their own choosing into the biological processes of health and disease. Historically, untargeted research has been the source of many of the best ideas and accomplishments of scientists at the Foundation, as well as researchers throughout the world.

OUR VISION acknowledges, reaffirms and celebrates the vision of founder Tom Slick Jr., who envisioned "a great center for human progress through scientific research." Our vision recognizes that success increasingly depends upon the synergistic contributions and energy of all its members – working together – in new ways.

It is a multidisciplinary community of respected scientists, educators and supporting staff members; with financial resources sufficient to achieve and sustain world-class scientific research; with strong networks of stimulating, collaborative contributors and learners; working in state-of-the-art facilities; with an administrative organization that is a model for achievement, scientific excellence and mission accomplishment.

OUR VALUES are truth, creativity, excellence and synergy. These values affect every aspect of the scientific enterprise involving the advancement of human health.

Representing a broad spectrum of disciplines, our scientists are turning today's research clues into tomorrow's medical advances. Southwest Foundation's national prominence as a biomedical research leader is directly attributable to the accomplishments of the scientists. In the truest sense, these scientists are the Foundation because they have dedicated their lives to advancing human health through scientific discovery.

About Southwest Foundation

As one of the world's leading independent biomedical research institutions, the Southwest Foundation for Biomedical Research is advancing human health. Today, SFBR's multidisciplinary team of nearly 75 doctoral-level scientists work together on more than 200 major research projects.

Located on a 332-acre campus in San Antonio, Texas, Southwest Foundation partners with hundreds of researchers and institutions around the world, targeting advances in the prevention and treatment of heart disease, diabetes, obesity, cancer, osteoporosis, psychiatric disorders, AIDS, hepatitis, malaria, parasitic infections and a host of other infectious diseases.

SFBR is the site of the Southwest National Primate Research Center and home to the world's largest baboon research colony. The Foundation enjoys a distinguished history in the innovative, humane and appropriate use of nonhuman primates for biomedical research.

SFBR was created through the philanthropic vision of Thomas B. Slick Jr. in 1941, and it relies on philanthropy to sustain it today. Seventy percent of its annual budget is funded from competitive, peer-reviewed grants, while another 12 percent comes from contracts with biotechnology and pharmaceutical firms. Remaining expenses must be met by the generous contributions of foundations, corporations and individuals, as well as earnings from SFBR's permanent endowment.

Southwest Foundation for Biomedical Research is dedicated to improving human health through research on the detection, cause, prevention, cure and eradication of disease. For more information, please contact the Foundation at (210) 258-9400, or visit our Web site, www.sfbr.org.

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