

**Southwest Foundation
for Biomedical Research**

**2002
report of progress in 2007**

SFBR



About SFBR

As one of the world's leading independent biomedical research institutions, Southwest Foundation for Biomedical Research is dedicated to advancing the health of our global community through innovative biomedical research. Today, SFBR's multidisciplinary team of 85 doctoral-level scientists work on more than 200 major research projects.

Located on a 332-acre campus in San Antonio, Texas, SFBR 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 diseases.

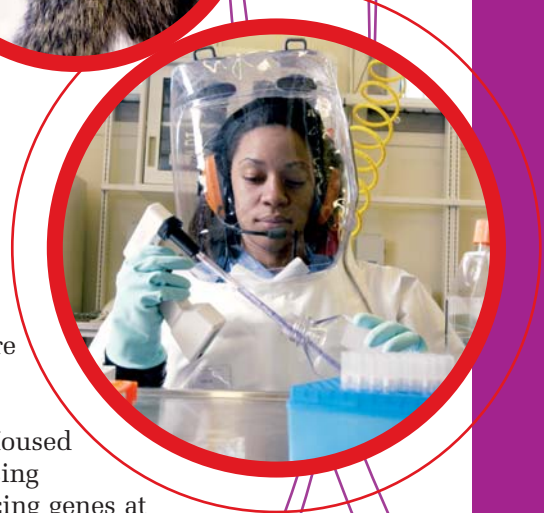
SFBR is the site of the Southwest National Primate Research Center and home to the world's largest baboon research colony, including a unique pedigreed baboon colony that is invaluable for genetic studies on complex diseases. The Foundation enjoys a distinguished history in the innovative, humane and appropriate use of nonhuman primates in biomedical research.

The Foundation also is home to other extraordinary resources that give its scientists and their collaborators an advantage in the search for discoveries to fight disease. With the nation's only privately owned biosafety level four (BSL-4) laboratory, designed for maximum containment, SFBR investigators can safely study deadly pathogens for which there currently are no treatments or vaccines.

Foundation scientists also have built the world's largest computing cluster for human genetic and genomic research. Housed in the AT&T Genomics Computing Center, the parallel-processing network allows SFBR geneticists to search for disease-influencing genes at record speed.

SFBR was created through the philanthropic vision of Thomas B. Slick Jr. in 1941, and it relies on philanthropy to sustain it today. Approximately 67 percent of its annual budget is funded from highly competitive, peer-reviewed federal research grants and contracts, while another 11 percent comes from commercial contracts with biotechnology and pharmaceutical firms. Philanthropy constitutes the second-largest portion of the Foundation's budget, as nearly one fifth of SFBR expenses are met by the generous contributions of foundations, corporations and individuals, as well as income and royalties from SFBR's endowment.

For more information on SFBR and its efforts to improve human health, contact the Foundation at 210-258-9400, or visit our Web site, www.sfbr.org.



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Credits

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LETTER FROM THE PRESIDENT



Transition and strength are two key words to describe Southwest Foundation for Biomedical Research at this point in its long and distinguished history. By nature, biomedical research institutions must have the agility to respond effectively to new challenges in health care and new opportunities that come from breakthrough ideas and advances in technology. They also must be able to adjust to the ebb and flow of federal funding that supports the vast majority of basic biomedical research. To do this successfully, they must have a solid foundation that can hold them secure in times of storm and provide a springboard for the launch of visionary initiatives.

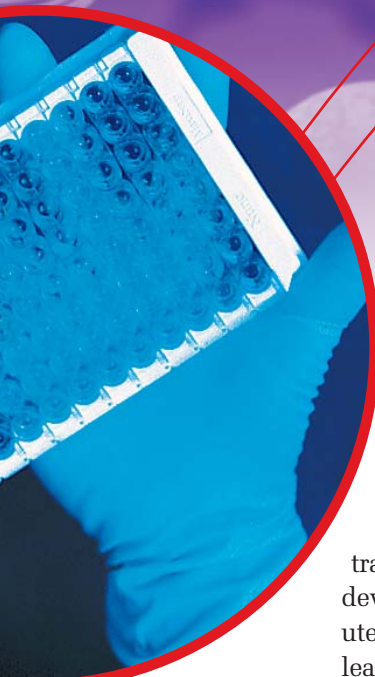
During my two years as interim president of SFBR, I have seen firsthand how the Foundation has responded with ingenuity to a research environment filled with both opportunities and challenges. I see even more how the organization's strong foundation, especially when combined with its visionary spirit, have propelled SFBR to a higher level of excellence that ensures a bright future for the organization and its contributions to human health.

This annual report coincides with the completion of my tenure as interim president, as we welcome Kenneth Trevett as Southwest Foundation's chief executive in September. Mr. Trevett comes to us from the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, or LA BioMed, where since 2001 he has served as president of one of the largest independent biomedical research organizations in California. Previously, he held senior management positions at such preeminent research institutes as The Schepens Eye Research Institute in Boston, an affiliate of Harvard Medical School; the Dana-Farber Cancer Institute in Boston; and The Jackson Laboratory in Bar Harbor, Maine. We are very pleased to have someone of his high caliber take the leadership reins at SFBR.

This leadership transition occurs at a time when the Foundation has completed another year of outstanding success. Despite a very difficult NIH funding environment that has caused a decline in federal funding at many research institutions across the country, SFBR has managed to "hold steady" and even see a slight increase in new grants and contracts over the past two years. The total of new federal grants awarded to SFBR grew from \$25 million in 2005 to approximately \$27 million in 2006 and 2007, while the total of all new grants and contracts – federal, commercial and philanthropic – held steady at \$32 million in 2005 and 2006 and rose to \$33.5 million in 2007.

This success in challenging financial times can be directly attributed to the ingenuity of SFBR scientists and the outstanding quality of their research. It also is a testament to the foresight of SFBR scientists, administrative leadership and donors, along with federal funding sources, as they worked together in the past to develop extraordinary resources that today give our scientists a true competitive edge. For example, the Southwest National Primate Research Center, the BSL-4 and other high-containment laboratories, and the AT&T Genomics Computing Center at SFBR are key enablers of our scientists' innovative research, in some cases allowing work to be done here that would be impossible elsewhere.

Likewise, today we're seeing the fruits of seeds planted nearly 20 years ago, when our geneticists initiated large population studies such as the San Antonio Family Heart Study, which involves



1,400 Mexican Americans from 40 San Antonio families. While this monumental study on the genetics of heart disease, diabetes and obesity has been a success in its own right, it also has allowed SFBR to spin off – and win federal funding for – a wide variety of new research efforts.

Speaking of spin-offs, SFBR successfully launched Evestra Inc. in early 2008, transferring its acclaimed Organic Chemistry Department to a new for-profit drug-development company focused on fertility control and the treatment of endometriosis, uterine fibroids and breast cancer. I am highly optimistic that Evestra will become a leading pharmaceutical company in the area of women's healthcare, with the potential to provide substantial returns to SFBR, its largest shareholder.

As financial investors are getting Evestra off to a strong start, other "investors" continue to provide vital support to Southwest Foundation. As an independent, non-profit research institute, we are heavily dependent upon philanthropy, and we have continued to be the beneficiaries of very generous contributions from individuals, foundations and corporations who believe in our mission. As an example, you will see in this report more than \$3.6 million in research grants awarded to SFBR from philanthropic sources in 2007. These types of grants are critical to our success, as they enable the highly novel and entrepreneurial types of research projects that have the potential for huge pay-offs down the road.

We also are seeing the benefit of a long-term effort to build the Foundation's endowment, which reached \$91.8 million at the end of 2007, up from \$86.2 million in 2006. Its growth has put the Foundation in a much stronger position as a non-profit biomedical research institute, especially when coupled with annual revenue from sources such as annual contributions from members of The Argyle and income from oil and gas properties left to SFBR by its founder, Tom Slick. The combined income from these two sources is the equivalent of another \$75 million in endowment, an enviable asset for an independent research institute with an operating budget of approximately \$50 million.

The scientific and financial strength of SFBR are greater now than at any time in the organization's history. I believe this, coupled with greater synergy and efficiency achieved through the recent organizational restructuring of both SFBR and the Southwest National Primate Research Center, means we are sure to see great things ahead for Southwest Foundation and its contributions to human health. Whether it be an adverse funding environment or the threat of emerging diseases, SFBR is well positioned to respond to the challenge.

Respectfully submitted,

John C. Kerr
Interim President





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LETTER FROM THE CHIEF SCIENTIFIC OFFICER

The Foundation continued in 2007 to capitalize on its scientific strengths to produce a large number of high-impact publications in the international scientific literature and to generate significant funding for major new research programs that will lead to the scientific discoveries of the future.

The building blocks of scientific progress are publications in the scientific literature. Publishing a peer-reviewed manuscript is a lengthy process that starts with the scientist investing years of effort in developing novel research strategies and garnering the funding to implement them, training technical staff to help with the work, conducting the research, analyzing the results, writing a manuscript, responding to peer reviewers' criticisms of the manuscript, and submitting one or more revised versions of it. If the manuscript is accepted for publication, more months will elapse before the building block is put in place in the form of a published manuscript that is available for the world of scientists to build upon with new ideas that may be triggered by that manuscript alone or in combination with others.

During 2007, SFBR had 32 principal investigators, and remarkably, they and their associates contributed 154 publications to the international scientific literature. Each of those publications adds a new increment of knowledge in one or another area of biomedicine, and some of them add critical new knowledge that will be essential for future medical advances.

A few of the key conclusions reported in the 2007 literature are as follows:

- ▷ A new method of quantifying expression levels of thousands of individual genes of people will enable the discovery of genetic variations that affect traits of medical importance (*Nature Genetics* 39:1208-1216, 2007).
- ▷ Immunization with particles that resemble hepatitis C virus results in control of hepatitis C virus infection in chimpanzees, paving the way for development of a hepatitis C vaccine for humans (*Proceedings of the National Academy of Sciences of the USA* 104:8427-8432, 2007).
- ▷ The cells that line the inside walls of arteries are damaged in baboons after only seven weeks of eating a typical North American diet with high levels of fat and cholesterol (*American Journal of Physiology-Heart and Circulatory Physiology* 292:H2913-H2920, 2007).
- ▷ The complete DNA sequences of the rhesus monkey and the laboratory opossum (*Science* 316:222-234, 2007; *Nature* 447:167-178) will greatly accelerate the pace of biomedical research using these vital animal model species, which are critical for many areas of biomedical research.

These articles are representative of the scores of scientific publications that present important discoveries in human subjects, as well as in the principal animal model species at SFBR: chimpanzees, baboons, rhesus monkeys, and laboratory opossums.

Whereas the publications and the research summaries in this report are the products of research that was conducted before and during 2007, the new grants awarded during 2007 reflect the new directions of research that will be pursued in the years ahead. Some of the 2007 grant awards are renewals of existing grants and will support novel research strategies in existing



research programs. Others support completely new avenues of research aimed at improving human health. It is a tribute to the caliber and perseverance of our 32 principal investigators that, despite major reductions in funding available from the National Institutes of Health, our principal source of revenue, new federal grants and contracts awarded to SFBR held fairly steady from 2006 to 2007, hovering near \$27 million. Two of the new awards, both from the NIH, exceeded \$3 million, and six others exceeded \$1 million.

The largest award was a \$3.7 million contract to Dr. P.N. Rao to continue operation of his steroidal drug synthesis laboratory in the Department of Organic Chemistry. With the transfer of that department to Evestra Inc. – the new for-profit pharmaceutical company of which SFBR is the principal shareholder – the funds remaining in the contract also are being transferred, providing a steady stream of revenue for this exciting new venture.

The other grant over \$3 million was awarded to collaborating principal investigators in the Department of Genetics and the Primate Center; the overall principal investigator for the entire program is based at the University of Texas Health Science Center at San Antonio. This program is investigating the effects of nutrient restriction in pregnant baboons on placental development and on fetal brain and kidney development. It is gratifying that investigators based in these two SFBR units and at UTHSCSA have combined their talents and expertises in this major program, which could not be conducted by any of them alone.

The Department of Genetics received three other NIH grants that each exceeded \$1 million. They support diverse areas of genetic research, including genetics of the malaria parasite and why some strains are more virulent and resistant to drugs than others; genetic determinants of susceptibility to thrombosis, or blood clotting, in Mexican Americans; and genetic determinants of Type 2 diabetes in Mexican Americans.

The Department of Virology and Immunology was awarded two grants of greater than \$1 million each, both focused on enhancing biodefense capabilities. One project aims to understand genetic mechanisms that control pathology induced by filoviruses, which include the deadly Ebola and Marburg viruses. The other will utilize a novel strategy for identifying safe and effective therapeutics for bioterrorism agents.

The Primate Center received one grant in excess of \$1 million, in addition to the grant supporting the collaboration mentioned above. It supports a breeding program to produce rhesus monkeys for AIDS-related research.

The prolific publication of results in high-impact journals combined with major successes in garnering new grant support are important metrics of past scientific productivity and the potential for future productivity, respectively. Many of the major research programs of SFBR have been developed over the last 15 to 25 years, and they are now reaching their full stride. The institution has never been in such a strong position to fulfill its mission to improve the health of our global community through innovative biomedical research.

I congratulate the scientists for their successes, and I thank the president, the Board of Trustees, and all of the supporters of SFBR for providing the necessary resources and an environment that is so ideally suited to the pursuit of scientific discovery.

Sincerely,

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

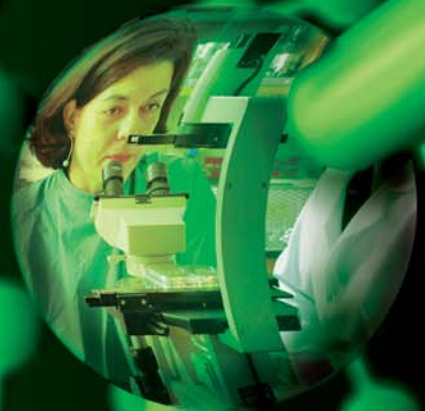


Biodefense



Women's Health

AIDS

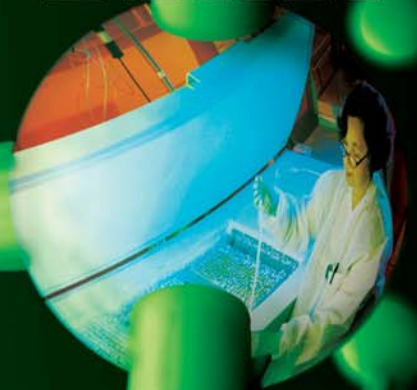


Nervous System Disorders

Cancer

Neglected Diseases

Heart Disease



SIFBR

A GLOBAL IMPACT

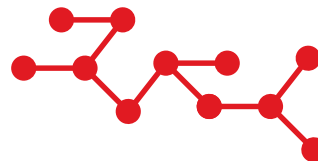
Few organizations have the potential for such immense worldwide impact as Southwest Foundation for Biomedical Research. In their efforts to advance the health of our global community through innovative biomedical research, SFBR scientists literally comb the earth searching for discoveries that could lead to new methods of diagnosing, preventing, treating and ultimately curing diseases that affect all our lives.

Their research projects take them from Alaska to Brazil and Texas to Thailand; from remote villages to the high-tech resources of genomic computing clusters and maximum containment laboratories; and from experiments on a Petri dish to pre-clinical trials with nonhuman primates.

The breadth of their research is equally as vast. In collaboration with hundreds of researchers and institutions around the world, they strive for advances in the fight against cardiovascular disease, diabetes, obesity, cancer, hepatitis, AIDS, bioterror threats, emerging diseases, mental illness, osteoporosis, pregnancy disorders, parasitic infections and a wide array of other human health problems.

Highlights of their research successes in 2007, along with the potential impact on the lives of people young and old, are described in the following scientific reports. As we commend them for their laudable efforts, we thank you, our many partners in progress, for joining SFBR in the fight to make some of today's greatest health threats a part of the past.

Working to stop the rising tide of heart disease, diabetes and obesity



Nearly one in every three deaths in the United States each year – almost 700,000 in total – is due to heart disease, making it the leading cause of death in this country and a major cause of disability, according to the Centers for Disease Control and Prevention. Without intervention, the problem seems destined only to worsen, as prevalence of obesity and diabetes – both of which greatly increase heart disease risk – continue to rise at alarming rates, both in adults and children.

Surveys conducted by the CDC from 1976-1980 and again from 2003-2004 indicate that, among adults ages 20 to 74, the prevalence of overweight and obesity in the United States has more than doubled, jumping from 15 percent to 32.9 percent during that period. Likewise, prevalence of overweight and obesity increased from 5 percent to 13.9 percent in children ages 2 to 5; from 6.5 percent to 18.8 percent in children ages 6 to 11; and from 5 percent to 17.4 percent in children ages 12 to 19.

The rise in obesity has been matched by a spike in Type 2 diabetes, which increased in prevalence by 13.5 percent between 2005 and 2007. According to the American Diabetes Association, 8 percent of the U.S. population, or 23.6 million Americans, are living with diabetes, and 57 million people have pre-diabetes. That is especially bad news when you consider that diabetes increases heart disease risk by two to five times.



How can we stop the epidemic?

Statistics such as those cited above have made Dr. Henry C. McGill Jr., senior scientist emeritus in the Department of Physiology and Medicine, a loud voice for societal changes. He warns that heart disease prevention requires the adoption of a healthy lifestyle beginning in youth. To put it more positively, as he and his colleagues wrote in a provocative paper accepted by the journal *Circulation* in December 2007 for publication in 2008, 90 percent of heart attacks could be prevented, and the best time to start prevention is in childhood. The paper is authored by Dr. McGill; Dr. C. Alex McMahan of the University of Texas Health Science Center at San Antonio and an adjunct faculty member of SFBR; and Dr. Samuel S. Gidding of the Nemours Cardiac Center, Alfred I. duPont Hospital for Children, Wilmington, Del.

Their conclusions are based upon evidence from multiple sources, including their own work with the Pathological Determinants of Atherosclerosis in Youth study, or PDAY, a national multi-center study begun in the 1980s. Cooperating pathologists collected the arteries and other tissues of about 3,000 young people ages 15 to 34 who died of external causes and were autopsied in medical examiners' laboratories. Central laboratories analyzed the samples for



the extent and severity of atherosclerosis (the build-up of fatty plaques in the arteries) and for the established risk factors for adult coronary heart disease: high blood cholesterol, high blood pressure, smoking, obesity and diabetes.

Analyses by Drs. McGill and McMahan and their colleagues over the years have resulted in numerous published papers showing not only that atherosclerosis starts to develop at an early age, but that these risk factors are associated with the extent and severity of atherosclerosis in the coronary arteries and the aorta. This has been affirmed by other studies in living young people showing that risk factors for heart disease measured in childhood can effectively predict levels of atherosclerosis measured 20 years later by x-ray and ultrasound.

In 2005, Dr. McMahan developed a tool for clinicians called a “risk score” for atherosclerosis, a single number that provided a weighted summary of the cumulative effects of all the risk factors to predict the likelihood of advanced atherosclerosis in young persons. Working with researchers from the Coronary Artery Risk Development in Young Adults study, Drs. McMahan and McGill showed that the risk score computed from risk factors measured between 18 and 30 years of age predicted calcium in the coronary arteries 15 years later. In 2007, they enlisted the cooperation of physicians in Finland who had followed about 1,300 children in the Cardiovascular Risk in Young Finns study and had measured atherosclerosis in the carotid arteries by ultrasound. The risk score measured in childhood and adolescence and



the change in risk score during adolescence were strong predictors of atherosclerosis 15 years later. All of this affirms the conclusions of Dr. McGill and his colleagues that the early control of risk factors for heart disease is the most effective way to prevent heart attacks in adulthood.

What do we do when lifestyle changes aren't enough?

While healthy lifestyles are the best way to prevent heart disease, diabetes, obesity, and many other metabolic disorders, what do you do when lifestyle alone is not enough? Both genes and the environment play critical roles in disease susceptibility, and some people are simply more prone to developing these disorders than others despite living a healthy lifestyle. Scientists will also tell you that our genes influence how our bodies respond to environmental factors, and the environment impacts the function of our genes.

In a modern environment that is contributing to a rapid increase in the prevalence of metabolic diseases, it is perhaps more important than ever to look for genetic factors that influence disease susceptibility with the hope of gaining insights into new targets for disease prevention and treatment. For example, if scientists can identify genes that play a protective role, medications might be designed to boost the activity of those genes, particularly in people who are at high risk. On the other hand, when genes are discovered that increase our risk, drug interventions might be designed to block their activity.

Scientists in the SFBR Department of Genetics made several breakthroughs in 2007 as part of their search for genetic factors that underlie obesity, diabetes and heart disease and for the associated biological pathways that might be targeted for the development of novel therapeutics. These findings relied

upon studies with various minority populations that have high rates of these metabolic disorders, as well as the pedigreed baboon colony at the Southwest National Primate Research Center (SNPRC).

Localizing genes that influence obesity

Obesity is rapidly escalating as a major health problem in the United States, where over 30 percent of the population is now considered obese. Obesity is a key risk factor for a multitude of other diseases including heart disease, hypertension, and diabetes. While obesity is unquestionably a major health problem for the general U.S. population, it is of particular concern among many minority populations and among children. Recent studies have demonstrated that almost 17 percent of children between 2 and 19 years of age are significantly overweight. Because obesity has increased despite the growing emphasis on healthy diet and lifestyle changes, other interventions are needed. Finding the genes responsible for obesity can suggest new pathways to target for its prevention and treatment. The critical genes to be targeted for development of new drug therapies may be those related to weight itself or to traits that lead to weight gain, such as appetite.

Focusing on the physical characteristics of total body weight and other related body traits, Drs. Laura Almasy and Jean MacCluer conducted a genome-wide scan in a Native American population to search for the genes that influence these obesity measures. An important finding was the localization of a novel gene influencing obesity on chromosome 4. This gene has not previously been implicated in obesity, so it may yield exciting new information on genetic contributions to obesity risk.

Genes that influence appetite may also be very important determinants of obesity. A variety of hormones influence whether or not we feel full after eating a meal. Research on the genetic determinants of such appetite regulators has been conducted in both human and nonhuman primate populations at SFBR by members of Dr. Tony Comuzzie's laboratory. In collaboration with investigators at the Baylor College of Medicine, Dr. Comuzzie localized a gene on chromosome 1 that is linked to variation in serum levels of ghrelin, a hormone associated with appetite and satiety. Interestingly, this same area of chromosome 1 has been implicated in the determination of levels of other weight-related factors, including insulin.

Cholesystokinin is a hormone that regulates food intake by acting as a signal to control portion size. Studies in the pedigreed baboon population at the SNPRC conducted by Dr. Comuzzie and his postdoctoral fellow Dr. Saroja Voruganti revealed that a gene located on chromosome 17 is linked to cholesystokinin. This area of chromosome 17 is also thought to harbor genes influencing other traits related to obesity, including Body Mass Index and leptin.

Localizing genes that influence diabetes

Type 2 diabetes, which is closely related to obesity, is also dramatically increasing in prevalence in many parts of the world; it currently affects about 10 percent of adults in the U.S. population. Until recently, this disease was considered an "adult onset" disease, but it is now being observed with increasing frequency in pre-teenage children, especially in minority populations such as the Mexican American population of San Antonio.

Finding the genes that influence diabetes-related traits can help in the



development of predictive diagnostic tests and in the development of new preventions and treatments for the disease.

Fasting glucose levels are commonly used clinically to determine risk for diabetes and diabetic state. In studies of Mexican American children, Dr. Tony Comuzzie of the Department of Genetics, in collaboration with investigators at Baylor College of Medicine, localized a gene influencing glucose levels to a region on chromosome 13. Similarly, a study of Mexican American adults revealed genetic factors on chromosome 2 that influence a trait used as a marker of progression of kidney disease in diabetes, glomerular filtration rate.

It has been observed that numbers of mitochondria, which are the power plants of the cell, are diminished in people with diabetes. Mitochondria are intimately involved in energy metabolism and response to oxidative stress. The role of mitochondria in disease development has become a fascinating new area of inquiry. In a novel investigation conducted at SFBR, Drs. Joanne Curran and John Blangero from the Department of Genetics localized two major contributing genetic factors influencing mitochondrial content, including one that is located on the maternally inherited mitochondrial genome. This innovative study was the first large-scale study of the inheritance of mitochondrial content and promises to identify specific genes that may be targeted to enhance mitochondrial robustness.

Localizing genes that influence risk for heart disease

As arguably the most important public health problem facing the nation, heart disease has been the primary focus of research on common complex diseases in the Department of Genetics since the department was formed in 1981. Building on a number of long-term studies conducted in baboon and human populations, these research efforts are yielding exciting new findings about the genetic determinants of heart disease and its risk factors.

Led by Drs. John Blangero and Jean MacCluer, SFBR geneticists located a number of genes related to common risk factors for heart disease, including hypertension, clot formation, cholesterol levels, and biomarkers for inflammation. Knowing where genes are in the genome is the first step toward determining the specific functional variants involved. Determining the functional variants is a crucial step toward using the genetic information for the development of new cures and preventions. In 2007, SFBR scientists reported two major advances toward the identification of functional variants within genes. First, an international collaboration between investigators at the *Hospital de la Sant Creu i Sant Pau* in Barcelona, Spain, resulted in the identification of the functional variants associated with plasma levels of Factors VII and VIII, which are highly correlated with risk of clot formation and with risk of heart disease.

In a highly significant paper, Drs. Laura Cox and John VandeBerg and colleagues identified the functional variants in a gene that regulates levels of high density cholesterol (HDL), which is commonly called the “good” cholesterol. Through investigations with the SNPRC’s pedigreed baboon colony, Dr. Laura Cox and colleagues identified the baboon endothelial lipase gene as a key determinant of HDL levels. They discovered this novel locus using an innovative combination of genomic, transcriptomic, and bioinformatic approaches. This major study was the first gene discovery effort that has moved from gene localization to gene identification in a nonhuman primate, representing a major step forward for genetic studies using nonhuman primate models of disease.





Neglected Diseases

Focus on neglected diseases has broad implications for human health

Diseases that affect fewer than 200,000 people in the United States are often described as orphan diseases. They are orphaned or neglected because of their perceived unimportance to public health compared to more common diseases that affect millions of Americans, such as heart disease, diabetes and cancer. Therefore, federal research dollars for orphan disease studies are hard to come by, and research efforts are few and far between.

However, as novel research efforts at SFBR have shown, attention to orphan and neglected diseases can be a tremendously valuable investment with a far-reaching impact. Certainly, research discoveries bring longed-for hope to Americans suffering from these diseases, but they also can facilitate improved control programs in countries where the diseases are more prevalent. And as at least one SFBR study shows, investigations and findings related to orphan diseases can sometimes have major implications for those common diseases that inevitably affect us or someone we love.

New approach to single-gene disorder sheds light on such diverse health problems as cystinosis, heart disease, Alzheimer's

A major breakthrough by SFBR geneticists in 2007 was made possible in large part because of donor funding that enabled investigators to take a never-been-done-before approach to studying a single-gene disorder and orphan disease called cystinosis.

Cystinosis, which affects only about 400 individuals in the United States, is caused by a defect in the *CTNS* gene, which results in the body's inability to transport excess amounts

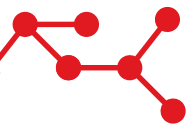
of the amino acid cystine out of cells. As the cystine accumulates to toxic levels, crystals form in the major organs of the body. If untreated, children with cystinosis generally die before age 10. Those who are treated face a challenging regimen of about 30 medications per day, administered at strict six-hour intervals, to treat the disease, its symptoms, and side effects of the various medications.

As with research on other single-gene disorders, most cystinosis research to date has focused solely on the gene that causes the disease and people affected by it. In a revolutionary approach that is set to become the new paradigm for the study of monogenic diseases, SFBR geneticists Drs. John Blangero and Eric Moses are leading an investigation that utilizes a large, unaffected population to examine the relationship of all the genes in the human genome to the *CTNS* gene. One important aim is to learn more about what the gene does in a healthy individual to lend insight into what goes wrong when the gene is disrupted. Another is to discover genes “upstream” from *CTNS* that affect its function; genes “downstream” from *CTNS* that are affected by it; and “parallel” genes that might perform similar functions. “Downstream genes” could potentially be good targets for treating disease symptoms and complications, while “upstream genes” might be used to help regulate *CTNS* and improve its function. “Parallel genes” might somehow be targeted to increase their function so that they can compensate for what *CTNS* fails to do in affected individuals.

As part of this research effort, which relies heavily on 20 years of accumulated samples, data and research conducted through the San Antonio Family Heart Study, Drs. John Blangero, Eric Moses and Joanne Curran embarked on the largest transcriptional profiling project ever undertaken by any research organization. They did genome-wide transcriptional scans – which reveal information about the output of every gene – of over 1,200 study participants. These transcriptional profile data allowed scientists to identify a number of genes downstream from *CTNS* that are potentially involved in determining disease progression in cystinosis.

In 2007, a landmark paper reporting the research approach and the first result from this novel study effort appeared in the prestigious journal *Nature Genetics*. In it, Drs. Harald Göring and John Blangero and their collaborators outlined how large-scale transcriptional profiling data can be used to speed the pace of gene discovery. Analyzing data on variation in HDL cholesterol previously generated for the participants in the San Antonio Family Heart Study in association with the transcriptional profiling data, Drs. Göring and Blangero discovered the gene *vanin 1 (VNN1)* and its significant effects on HDL.





The *VNN1* finding has clear implications for heart disease, in which HDL cholesterol plays a protective role, but it also provides hope to patients suffering from other diseases. *VNN1* is known to produce cysteamine, which helps transport excess cystine out of cells. Cysteamine also removes other dangerous things from cells, including excess glutamine, which can lead to Huntington's and Alzheimer's. It currently is being tested as a treatment for both of those diseases, as well as for major depression.

The new findings about *VNN1* by SFBR scientists are therefore expected to give pharmaceutical companies good reason to pursue drugs that could increase the gene's activity, stimulating it to produce more cysteamine naturally. That could result in new preventions and treatments for a variety of disorders, and it could reduce the need for cystinosis patients to take cysteamine orally, allowing them to say "goodbye" to the drug's terrible side effects.

Beyond *VNN1*, the powerful new discovery method used by SFBR scientists to quickly find this gene can be and is already being applied to the search for genes that influence a wide variety of health problems. That means that many more important genetic discoveries are well within scientists' reach.

Genetic studies of neglected parasitic diseases yield new tools for addressing the health problems of the developing world

While not major health problems in the United States, parasitic diseases persist as major health concerns for much of the developing world. These neglected diseases can affect up to a quarter of the world's population, as is the case with intestinal worm infections. The Department of Genetics has a major research program in the area of genetics of susceptibility to many of these neglected parasitic diseases.

Chagas disease. Chagas disease is the leading cause of heart disease throughout Latin America, where it affects about 17 million people. The disease is a severe public health problem because there are no vaccines or prophylactic drugs, and there are no effective therapies for the chronic long-term phase of the disease. Between 100 million and 120 million individuals are considered to be at risk for infection with *Trypanosoma cruzi*, the parasitic organism that causes Chagas disease.

Unfortunately, Chagas disease also is emerging as a significant health threat in the United States, where there have been recently reported cases of disease acquired from the triatomine bugs that transmit *T. cruzi* and which are common in the Southwest. Furthermore, it has been estimated that more than 100,000 Latin American immigrants to this country are chronically infected with *T. cruzi*, which presents a major concern for blood and tissue banks.

A research program directed by Drs. Sarah Williams-Blangero and John VandeBerg is focused on assessing the genetic determinants of susceptibility to Chagas disease. It is clear that genes play a key role, since only about 30 percent of individuals infected with *T. cruzi* develop heart disease.

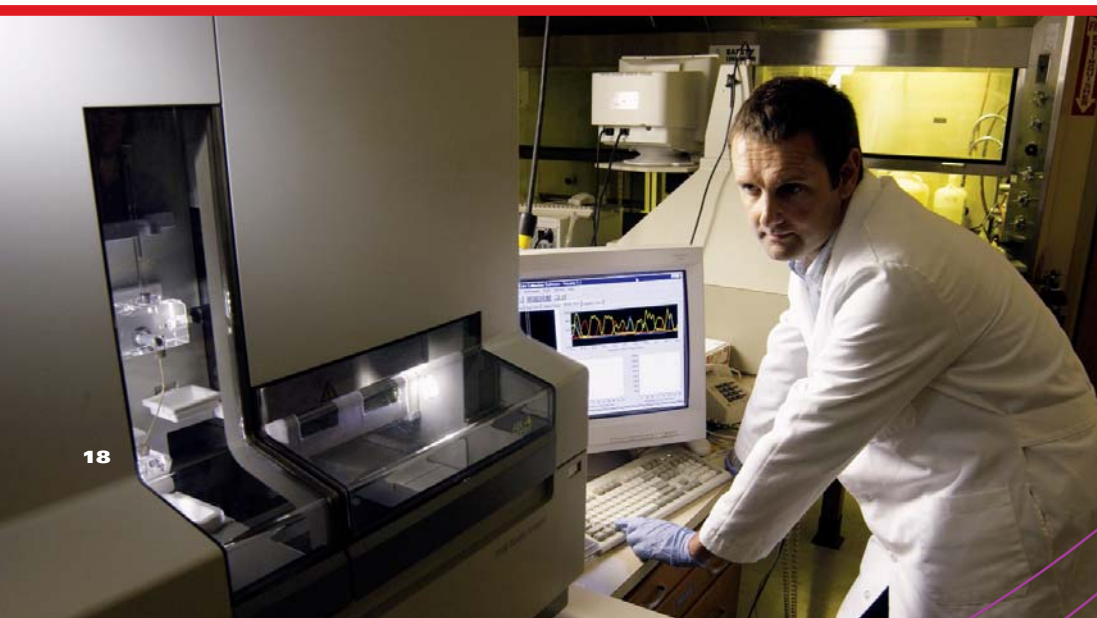


During 2007, in one of the largest studies of Chagas disease epidemiology conducted to date, Drs. Williams-Blangero, VandeBerg, and colleagues documented that individuals seropositive for *T. cruzi* infection in rural Brazil had higher rates of electrocardiographic anomalies than seronegative individuals. They are now pursuing the genetic components to these cardiac consequences of long-term infection with the parasitic organism *T. cruzi*. Parallel work is ongoing in SFBR's nonhuman primate populations, where *T. cruzi* infection naturally occurs at a low rate. A key purpose of this effort is to find predictors that an infected individual will go on to develop disease. That way, those most at risk could receive available treatments, and those not at risk could be spared the side effects of these highly toxic drugs.

Worm infections. During 2007, SFBR geneticists made significant progress in developing tools for the study of worm infections, which affect a huge proportion of the world's population but remain neglected as research foci. Investigators at SFBR have been studying the genetic determinants of susceptibility to worm infection in a Jirel population of Nepal for the last 15 years. Now, Dr. Charles Criscione has made it possible to extend this study to considering the influence of genetic variation in the parasite on risk for infection. A postdoctoral scientist working with Drs. Tim Anderson and Sarah Williams-Blangero, Dr. Criscione developed 35 genetic markers for roundworm collected from Jiri, Nepal. The markers that Dr. Criscione developed provide critical tools that will allow investigators to explicitly consider the influence of genetic variation in the parasite on risk for infection, potentially leading to a fuller understanding of the dynamics of infection and new insights for prevention and treatment.

Schistosomiasis. Schistosomiasis, which affects over 200 million people throughout the world, results from flatworm infection and can lead to malnutrition, anemia, and enlargement of the liver and spleen. While the disease is infrequently fatal, the long-term chronic illness is extremely debilitating and significantly affects capacity for physical labor, resulting in major economic consequences.

It is known that genetic factors within the parasites influence a number of traits relevant to the epidemiology of the disease, such as drug resistance and transmissibility. However, attempts to identify the specific parasite genes affecting these traits have been hampered by the lack of availability of a gene map for this species. In 2007, Dr. Timothy Anderson obtained NIH funding to support the development of the first genetic linkage map for *Schistosoma mansoni*. This exciting project will allow powerful linkage approaches to be used for the detection of genes influencing drug resistance and a broad range of other traits in future studies of *Schistosoma mansoni*.





Cancer

Fighting off cancer – before and after it appears

“You have cancer.” Those are dreaded words, and unfortunately, they’re all too common in society today. According to the American Cancer Society, the lifetime risk of developing cancer is slightly more than 1 in 3 for women and slightly less than 1 in 2 for men.

How can we take the fear out of those words? At Southwest Foundation for Biomedical Research, scientists are tackling that problem on complementary fronts. One novel approach aims to make the diagnosis less common by defeating a cause of cancer before it leads to the disease, while another searches for novel and more effective ways to treat cancer that has already developed.

Getting at the root of the problem

When you hear the word “hepatitis,” you don’t necessarily think of cancer, but hepatitis B and C are the most common causes of liver cancer in the United States. And while deaths from cancer of all causes decreased 1.1 percent per year between 1993 and 2002 in the United States, death rates from primary liver cancer (hepatocellular carcinoma, HCC) increased by annual rates of 3 percent among white men, 4.5 percent among black men, 3.7 percent among white women, and 5 percent among Hispanic women. Primary liver cancer is not among the most common cancers in the United States, but it ranks eighth among leading causes of cancer death because the average time from diagnosis to death is one year due to the lack of effective treatments.

Dr. Robert Lanford, a scientist with the SFBR Department of Virology and Immunology and a core scientist with the Southwest National Primate Research Center, is the principal investigator of an NIH grant examining the mechanism of viral clearance of hepatitis B virus (HBV) in chimpanzees and the long-term effects of chronic infection with HBV. The study involves collaborators at the Fox Chase Cancer Center in Philadelphia, the University of Adelaide in Australia, and the NIH. Together, they are performing the most detailed analysis of HBV infections ever conducted in hopes of finding better approaches to treating chronic infections and possibly a better understanding of how this virus causes cancer.

One of the key strengths of their studies is that they have developed the methods needed to follow the fate of individual cells in the liver. They essentially found a way to identify a fingerprint that is unique for every cell, and by following those fingerprints, observed that some cells have a selective advantage. Rather than being killed off by a hepatitis B infection, they not only survive but continue to divide and replicate, often forming large clusters of identical new cells. Dr. Lanford believes these large clusters set the stage for cancer to develop, since they are susceptible to DNA damage from the oxidative environment in the liver caused by HBV infection. He considers this discovery a major breakthrough, because every time you increase understanding of how cancer gets started, you increase the potential to find new cures.

Efforts to cure or prevent infection with viruses that cause cancer

In other studies with the hepatitis C virus (HCV), Dr. Lanford is looking for new methods to cure the infection. The best way to prevent liver cancer is by curing the infection before the cancer starts, just like stopping smoking is the best method to prevent lung cancer. Using the chimpanzee model of HCV, his research team is evaluating many of the new drugs being developed by pharmaceutical companies to treat HCV infection. Each year, his laboratory evaluates five to 10 drugs that, if successful in the chimpanzee model, will progress to human clinical trials. Five years ago, very few of these drugs showed good potency for inhibiting HCV infection in the chimpanzee, but today, most of the drugs decrease the amount of virus in the blood by 10,000-fold in just a few days. The problem is that the virus becomes resistant to any single drug used alone, so the trick is to develop a cocktail of inhibitors that uses





multiple approaches to corner the virus. This is the same philosophy used today in combating HIV infections. The difference is that, although HIV can only be treated and kept under control, a good multi-drug cocktail could actually cure most hepatitis C infections. And if you can cure HCV, you can prevent the cancer it often causes.

Dr. Krishna Murthy is another SFBR investigator working in the area of hepatitis C prevention, particularly through efforts to develop HCV vaccines and test them in the chimpanzee model. In a collaborative study with Dr. Chris Walker of The Ohio State University, he recently demonstrated that the depletion of specialized immune cells during the acute phase of infection results in progression to chronic infection in chimpanzees. This finding, published in 2007 in the *Proceedings of the National Academy of Sciences of the United States of America*, is being followed up by current studies evaluating vaccine strategies to induce and activate those specialized immune cells with the aim of preventing HCV infection.

The search for new cancer-fighting drugs

The discovery of new drugs that might be useful for the treatment of cancer is an important research focus at SFBR, as scientists strive to find more effective and less toxic ways to fight the various forms of the disease, as well as to offer treatment alternatives to individuals whose cancer is resistant to existing drugs. Significant progress was achieved in this effort in 2007.

JG-03-14. Dr. Susan Mooberry in the SFBR Department of Physiology and Medicine leads a cancer drug discovery program focused on the exploration of natural compounds from plant and marine life as well as synthetic compounds that mimic and improve upon compounds found in nature.

Recently, her laboratory entered into a collaboration with Dr. John Gupton of the University of Richmond to evaluate a series of synthetic compounds that mimic natural products. After several members of the compound class were found to be effective in killing cancer cells, further tests were conducted to reveal the compounds' mechanism of action, or

how they kill cancer cells. It was discovered that these compounds are tubulin-binding microtubule agents. In other words, they disrupt the action of microtubules, a cellular structure that is vital to the cell division process, and thereby cause the cancer cells to turn on a cellular suicide program that causes their own demise.

The best compound in the class, designated JG-03-14, was found to be highly potent, and it was effective against cancer cells that are multi-drug resistant to some of the most widely used chemotherapeutic drugs used today. In a mouse model of prostate cancer, the compound also showed good anti-tumor actions.

The entire series of compounds was evaluated for biological activities and then modeled by Dr. Glen Kellogg of Virginia Commonwealth University to predict how they bind within the colchicine binding site on tubulin. This provides information that is helpful to the research team as they work to develop new analogs with better drug-like properties. Already, new JG-103-14 analogs with optimal drug-like properties have been designed and modeled. Now they will be synthesized and tested to identify a clinical drug candidate. This work led to the publication of two peer-reviewed journal articles in 2007.

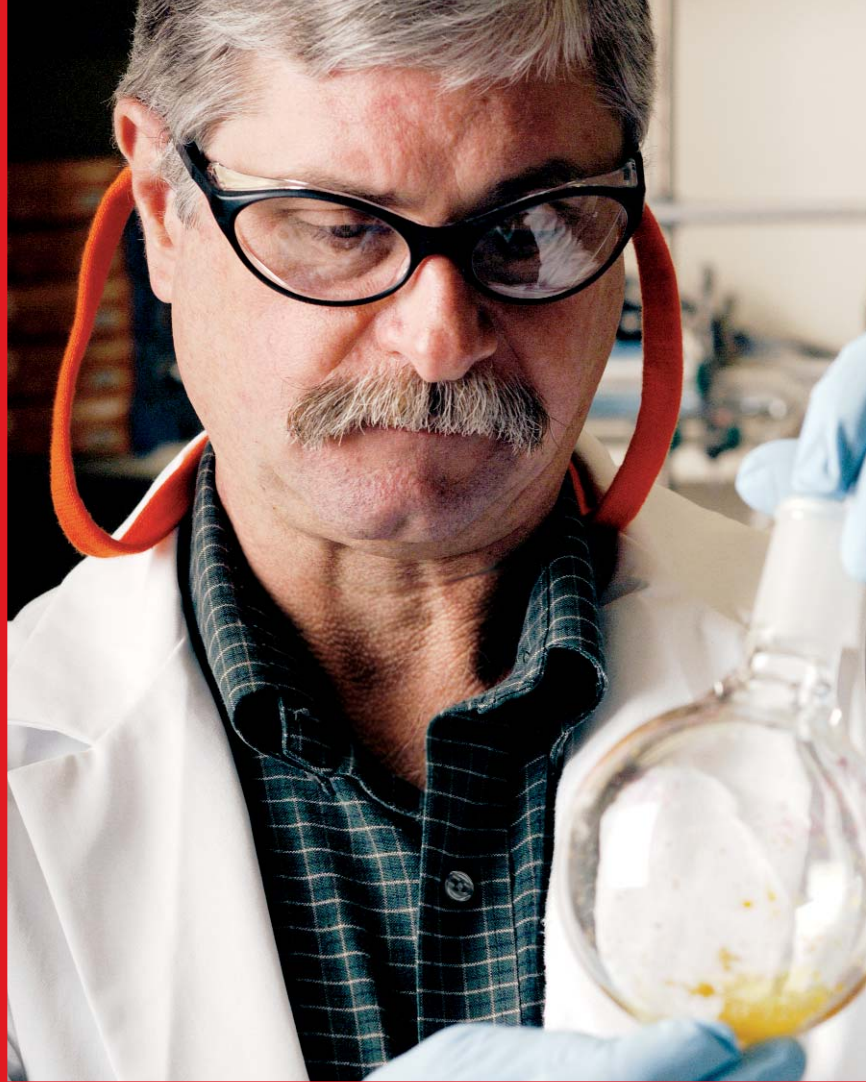
Other drug development efforts. In other efforts to find new and improved products for treating cancer, Dr. Mooberry is collaborating with Dr. Moses Lee at Hope College in Michigan to identify and synthesize new compounds that are as effective as but less toxic than combretastatin, which has been shown not only to kill cancer cells but also to destroy the network of new blood vessels that tumors need to support their growth. She also continues work with Dr. Phil Crews at The University of California, Santa Cruz, and Dr. Paul Wender at Stanford University to further develop and test the laulimalides, a new class of compounds discovered through Dr. Mooberry's screening program to work like the cancer drug Taxol. In 2007, laulimalide was found to have good activity against a colon cancer model.

Efforts to personalize cancer treatment

With funding by a pilot study grant from the Max and Minnie Tomerlin Voelcker Fund in 2007, SFBR has started applying the powerful resources and expertise of its Genetics Department toward an effort to help improve the survival chances of each individual diagnosed with cancer. How? By initiating an investigation to uncover genetic factors that influence individual variation in response to cancer-fighting drugs.

Although much of the variability in response to chemotherapy can be attributed to drug interactions as well as environmental and clinical factors, there is evidence that people's genes influence their individual response to chemotherapy, both in terms of how effective certain drugs are in treating their disease and in the severity of side effects they suffer. With this in mind, Drs. John Blangero, Joanne Curran and Melanie Carless are using state-of-the-art genomic methods to identify novel genes that influence this individual variation.

The results could ultimately be used to develop more effective individualized medical interventions for cancer patients, as treating physicians would have valuable information needed to determine which chemotherapy methods will be the most effective for a particular patient, and avoid critical time experimenting with treatments to which the patient will not respond well. New and more effective cancer drugs might also be designed based on information learned about the interplay of cancer and genetics.



W o m e n ' s H e a l t h

New venture promises benefits for women's health

The past year has been an exciting one for SFBR, as efforts to spin off one of its longest-running and most highly respected research departments have paved the way for a wide variety of developments in the area of women's health.

In early 2008, SFBR established Evestra Inc., transferring its Department of Organic Chemistry to this new for-profit pharmaceutical company, which will focus on the development of new products for contraception; safer hormone replacement therapy; the treatment of endometriosis and fibroid tumors; the treatment of hormonally dependent breast cancer; and other women's health issues.



The new venture might be described as a win-win-win situation.

For women, it means that a world-class team is pushing full steam ahead with the development of new drugs to save and improve their quality of life.

For SFBR, the majority stockholder in the new company, it means there are potential financial gains as the value of its holdings increases. That will benefit the Foundation's endowment, which provides a source of support for all of SFBR's basic, not-for-profit biomedical research.

And for the members of the Department of Organic Chemistry, it means they now have a tremendous opportunity to take the large body of work they have accumulated, along with their sense of innovation, and apply it toward the development of marketable healthcare products under the guidance of an expert management team operating in both San Antonio and Germany.

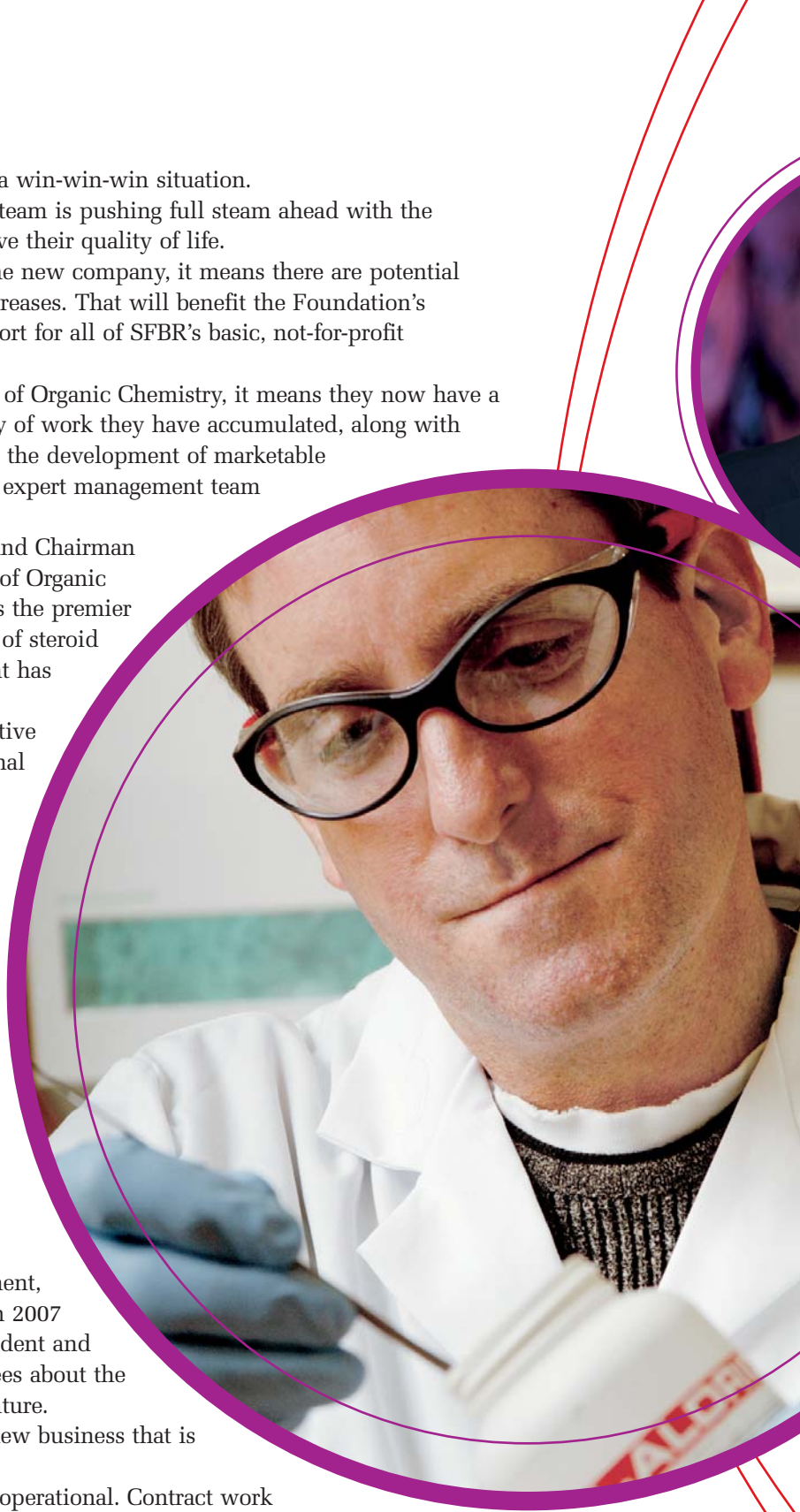
Under the direction of Senior Scientist and Chairman Dr. Pemmaraju N. Rao, the SFBR Department of Organic Chemistry has consistently been recognized as the premier research group in the nation for the synthesis of steroid hormones. In fact, for 32 years, the department has continually held competitive contracts as The Chemical Synthesis Facility for the Contraceptive and Reproductive Health Branch of the National Institute of Child Health and Human Development.

Over the years, the group has developed synthetic methods for the reproduction of hundreds of steroids and other compounds that have been investigated for the development of safer and more effective methods of contraception as well as for the diagnosis and treatment of a variety of reproductive disorders and even cancer. Dr. Rao and his team hold 17 patents in these areas, with more pending. One compound developed by Dr. Rao's team was licensed to industry and is currently in Phase III clinical trials for the treatment of endometriosis and uterine fibroids.

Seeing the great potential of the department, SFBR President John C. Kerr began meeting in 2007 with Dr. Rao and Dr. Ze'ev Shaked, now president and CEO of Evestra, and the SFBR Board of Trustees about the possibility of spinning it off as a for-profit venture.

The result has been the launching of a new business that is far beyond a traditional start-up.

Laboratories and equipment are already operational. Contract work from the NIH is already in place to provide a steady stream of income. A large body of patented, scientific work already exists. And the vision already is laid for a solid pipeline of pharmaceutical products, with plans to pursue a capital-efficient short-term and long-term drug development strategy. The short-term strategy is based on the reformulation of existing, approved steroid-based pharmaceutical products. The long-term strategy involves the in-house





development of novel steroidal drugs based on the expertise of the organic chemistry team. And last but certainly not least, a powerful and experienced management team is in place to guide the business to success.

Dr. Rao, senior vice president of research for Evestra, now works with:

- ▷ **Ze'ev Shaked, Ph.D.** – Evestra president and CEO. Before founding Evestra, Dr. Shaked was chief operating officer of ILEX Oncology and president of ILEX Products Inc. and held a number of senior R&D and management positions with other pharmaceutical companies, including Spherics Inc., ImmuLogic Pharmaceutical Corp., Berlex Biosciences Inc., Triton Biosciences Inc., CODON Corp. and Chiron Corp. He has extensive experience in the development of biologics and conventional drugs.
- ▷ **Klaus Nickisch, Ph.D.** – chief scientific officer and managing director, Evestra-Germany. Dr. Nickisch spent over 28 years with Schering, AG, one of the leading international pharmaceutical companies, in a wide range of positions before the recent merger of Schering with Bayer. Beginning as a medicinal chemist, Dr. Nickisch moved from research to product development and project management, leading a number of major programs in oncology and female healthcare and finally serving as senior vice president and head of global project management.

The Evestra Board of Directors consists of Kerr, J.R. Hurd (chairman of the SFBR Board of Trustees), Dr. Shaked and Dr. Nickisch.

Evestra also boasts an impressive Scientific Advisory Board. Chaired by Dr. Nickisch, its other members include Dr. Rao and a team of experts from the United States and abroad:

- ▷ **Walter Elger, M.D.** – former head of Female Health Research, Schering AG and Jenapharm
- ▷ **Irving Spitz, M.D., Ph.D.** – director of the Institute of Hormone Research in Jerusalem, emeritus professor of endocrinology at Ben Gurion University in Israel, and adjunct professor of medicine at Weill Medical College of Cornell University
- ▷ **Werner Raff, M.D.** – former head of Female Health SBU, Schering AG
- ▷ **James W. McGinity, Ph.D.** – professor and division head of Pharmaceutics, College of Pharmacy, University of Texas at Austin
- ▷ **Robert Shenken, M.D.** – University of Texas Health Science Center at San Antonio, chair of the Department of Clinical Gynecology

“One rarely sees a new company being formed with such an impressive scientific and management team,” said Kerr. “Truly, each of these men is world class in his own right. Their coming together for this new venture presents us with a tremendous opportunity to build a company that will be an industry leader in the area of women’s health and cancer treatment.”

From pregnancy to aging disorders, other efforts in women’s health at SFBR make significant progress

While the spin-off of the Organic Chemistry Department to Evestra Inc. holds great promise for women’s health issues, so do ongoing research projects in other SFBR departments. Two projects in the Department of Genetics that made great strides in 2007 are of import to young and old, as they lend insight to a common pregnancy disorder and the increasing problem of osteoporosis.

Discovering novel genes that influence hypertension in pregnancy

Preeclampsia is the most common major disorder of human pregnancy and can lead to serious health consequences for both mothers and children. Despite its frequent occurrence, the cause of preeclampsia remains unknown, leaving few options for treatment other than rest and, if necessary, pre-term delivery of the baby. However, it is clear that genetic factors play an important role in preeclampsia, which runs in families, and Dr. Eric Moses is on a mission to uncover which genes, in particular, affect a woman's susceptibility to the disorder. That information could lead to improved prevention and treatment options that deal with the cause of preeclampsia rather than just its symptoms.

Dr. Moses' program involves a network of international collaborations and brings together leading experts in genetics and obstetrics as it utilizes data from a number of different populations, including an Australian study population that involves three generations of family members and a case-control cohort from Norway. The research group made significant progress in 2007.

A study in the Norwegian population revealed that an allele of the inflammatory response gene *SEPS1* (a gene originally discovered by SFBR investigators) was a significant risk factor for preeclampsia. In collaboration with investigators at the Royal Women's Hospital in Melbourne, Australia, Dr. Moses' group has localized a susceptibility gene on chromosome 2 that is now the focus of a current NIH-funded project. They also have recently localized two novel genes influencing susceptibility to preeclampsia in the Australian families. With the knowledge of the chromosomal locations of these genes, they have identified strong potential candidate genes at all three chromosomal loci which may be the genes influencing preeclampsia.



Uncovering the genetic components of osteoporosis

Foundation scientists are also working to understand the genetic factors influencing osteoporosis, which although it also can affect men, is a particular health concern for many older women. Osteoporosis is caused by the loss of bone mineral density and is known as fragile bone disease, because it weakens the bones and increases susceptibility to fractures. More than 10 million people in the United States are currently affected by the disorder, and that number is expected to increase exponentially as the population ages. Therefore, new methods of preventing the disorder – or at least lessening its severity – are sorely needed.

Drs. Lorena Havill and Michael Mahaney are spearheading a major research effort aimed at assessing the genetic determinants for osteoporosis. This innovative work involves both human and baboon populations and employs a variety of experimental and genetic epidemiological approaches in the quest to discover genes that may be targeted for the development of new preventions and treatments.

During 2007, the scientists analyzed a variety of bone-related traits in a Hutterite population from South Dakota. The Hutterites are members of a religious group that lives communally, and as a result, all members have similar lifestyles and diets. This relatively constant environment, combined with the complex family relationships among members of Hutterite communities, make these populations ideally suited to genetic analysis. The work conducted with this population revealed high heritabilities for many bone-related traits. For example, between 40 percent and 62 percent of the variation in bone mineral content and bone mineral density was found to be attributable to genetic factors. Mechanical properties of bone can also affect the susceptibility or resistance of bone to fracture, and through stress tests with bones collected from deceased baboons in the Foundation's pedigreed colony, Dr. Havill demonstrated that 64 percent of the variation in bone toughness is attributable to genetic factors. Now Drs. Havill and Mahaney want to find out which particular genes are involved in these risk variations, since drugs to target those genes may provide another means of maintaining or improving bone strength and resistance to fracture.



B I O D E F E N S E

Scientists enter a brave new world as they strive to fend off bioterrorism and emerging infectious diseases

With the terror attacks of Sept. 11, 2001, and the anthrax-laced mailings that followed that same October, the threat that terrorists might use biological weapons to attack the U.S. population became all too real.

Nature, too, has presented new challenges, especially when coupled with a global economy and international tourism that make for the easy transport of disease from one nation or continent to another. Infectious diseases such as West Nile virus and dengue fever have made their way to the United States as other emerging diseases such as SARS and avian flu have threatened to do the same. Likewise, other deadly viruses such as Ebola, Lassa and Marburg have continued to cause periodic disease outbreaks in Africa, creating additional concern about the need for their containment.

Fortunately, a group of key defenders has been ready and able to respond. Donning protective space suits rather than military uniforms and entering a maximum containment

laboratory rather than a tank or a jet fighter, SFBR scientists have embraced and expanded upon a mission they started well before 9-11: developing and testing potential diagnostics, vaccines, and treatments for some of the world's deadliest pathogens.

With the nation's only privately owned biosafety level 4 (BSL-4) laboratory, several BSL-3 labs, appropriate scientific expertise, and the invaluable animal models and veterinary expertise of the Southwest National Primate Research Center, SFBR has quickly moved to the forefront of biodefense research, an area in which its scientists made great strides in 2007.

Developing improved methods of detection

Before you can fight to defend yourself against something, you need first to know it's there. That is especially true for deadly diseases such as Marburg and Ebola, which can cause horrific outbreaks of highly lethal hemorrhagic fever, but for which no treatment or vaccine exists. Prevention is currently the only means of defense, creating an urgent need for effective diagnostic tests capable of detecting and identifying tiny amounts of these viruses before they even cause symptoms. That would allow effective quarantines to be implemented to limit the spread of these diseases.

The problem is that current diagnostic tests can be slow, complex and expensive, all factors that limit their use on a large scale in the United States or in areas where the viruses are endemic, such as Africa. Furthermore, these systems require a "cold-chain," such as refrigeration for storage before use, which limits their widespread distribution, especially in the remote areas where outbreaks typically occur.

For help with this type of defense, SFBR virologist and antibody engineer Dr. Andrew Hayhurst has been designing a special type of soldier: nanobodies – or literally, small antibodies – derived from llamas and selected to recognize live Marburg virus preparations within the BSL-4 laboratory. These nanobodies are incredibly heat stable – they can even be boiled – which will enable diagnostics into which they are incorporated to be very rugged and bypass the need for a cold-chain. Dr. Hayhurst and his colleagues have determined that the Marburg-specific nanobodies all target nucleoprotein, which is not only a major component of the virus particles but is able to self assemble to form a long stringy polymer consisting of hundreds of nucleoprotein molecules. They believe the nanobodies and polymer bind to each other much like Velcro, in that a multitude of weak contacts can generate a very strong interaction. It is this strength that enables exquisitely specific and sensitive Marburg virus detection.

In order to better understand this phenomenon and to expand the usefulness of their findings, they have applied the method to the four different species of Ebola virus. These are close relatives of Marburg, share similar structural features and have similar ominous disease potential. Encouragingly, Dr. Hayhurst and his peers have found that all the resulting nanobodies recognize Ebola nucleoprotein, and several allow concise species detection. Consequently, they have discovered a common mechanism to realize the sensitive detection of both Marburg and Ebola viruses. In so doing, they may also have assembled an army of antibodies having the potential to interfere with viral assembly, so they are now starting to investigate this novel therapeutic avenue.





Successful tests with preventive vaccines

The old adage that an ounce of prevention is worth a pound of cure still holds true today, which is why SFBR scientists are heavily involved in efforts to help develop and test effective vaccines for bio-threat agents. A major leap forward was made in this effort in 2007, as Dr. Ricardo Carrion Jr. and other SFBR researchers collaborated with investigators at Emory University to develop and test a candidate Ebola VLP vaccine. VLP stands for “virus-like particle,” meaning that the vaccine is based upon proteins expressed in the laboratory that assemble into a particle that looks like the Ebola virus but does not cause disease. Tests in SFBR laboratories showed the vaccine to be effective in protecting both mice and guinea pigs from an otherwise lethal infection of Ebola. Since multiple doses of the vaccine were needed to confer this protective immunity, investigators are now working to increase its immunogenicity, hoping to make it effective with just a single dose.

The hunt for treatments and cures

While many SFBR investigations focus on the development and testing of potential novel treatments for emerging diseases and bio-threat agents, a new study begun in 2007 aims to discover whether cures for these dangerous pathogens already exist. Working with Silicon Valley-based SRI International (Stanford Research Institute) and other national collaborators, SFBR investigators are participating in a study aimed at identifying approved drugs that could also be effective against biological threats. The goal of the program – funded by the Defense Threat Reduction Agency of the Department of Defense – is to repurpose drugs that are currently FDA-approved and marketed but have not been previously evaluated against diseases caused by biological weapons.

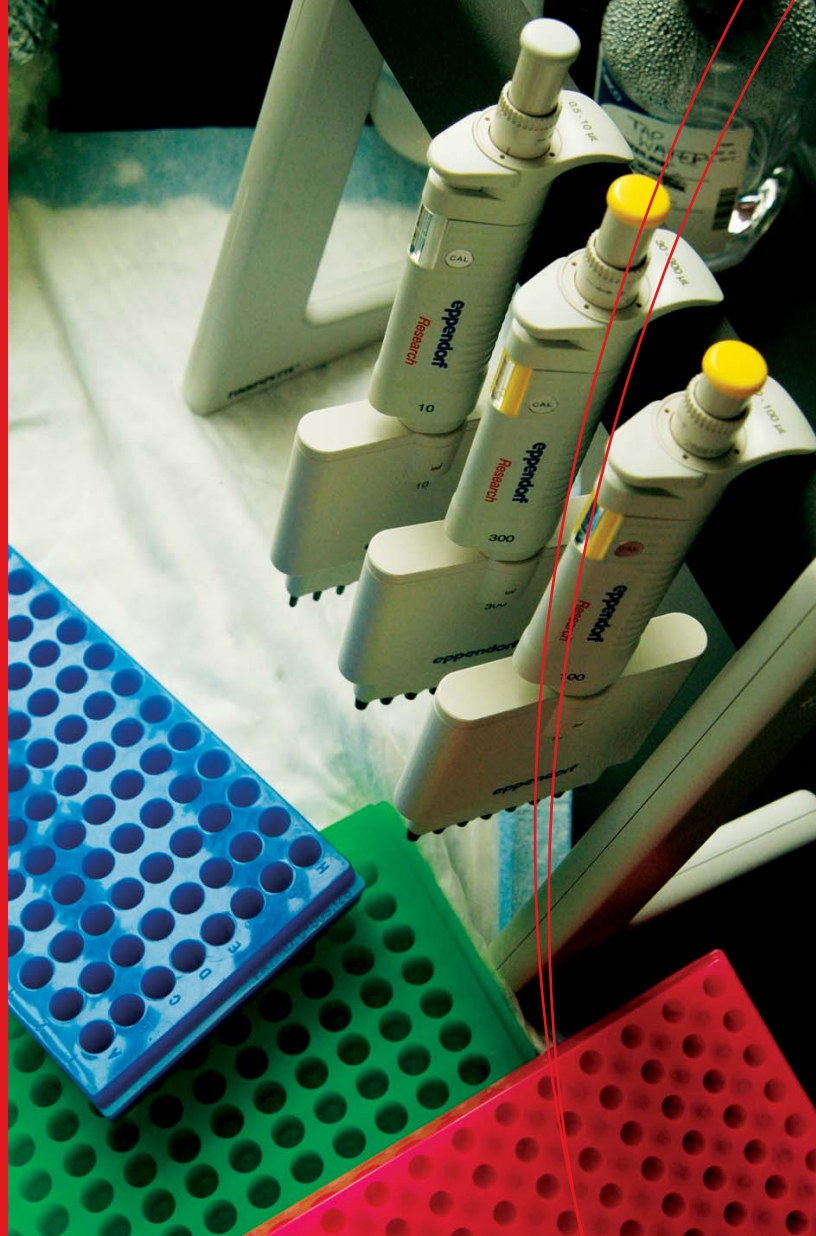
Dr. Ricardo Carrion Jr., who heads the subcontract to SFBR on this project, is enthusiastic about the possibilities, noting that with nearly 10,000 drug compounds known to clinical medicine, there is great potential that some of them could be effective against bio-threat agents such as Ebola, Lassa, Marburg, anthrax and tularemia.

With BSL-4 capabilities and expertise in biodefense research with animal models, SFBR’s efforts in this project will be to validate leading “hits” identified through screening by fellow collaborators. Positive results in SFBR laboratories could put one or more of these drugs on a speedy course to approval for use in the event of a biological attack.

Development of new animal models and research methods

With a unique combination of extraordinary resources that includes the nation’s only privately owned BSL-4 laboratory and the Southwest National Primate Research Center, SFBR





plays a leading role in the development of new animal models for biodefense research. This is of critical importance, since human studies with candidate vaccines and treatments in this area can be unfeasible and unethical. The Food and Drug Administration has therefore enacted what is known as the “Two Animal Rule,” which states that a biodefense drug that proves safe and effective in at least two animal models can be approved for development and stockpiling for use in the event of a national emergency. Especially in this case, it is important that one of the models used in scientific investigations be a nonhuman primate, which most closely resembles humans in genetics and physiology and therefore is most likely to mimic human disease processes and responses to vaccines and drug therapies.

In 2007, SFBR virologists Dr. Jean Patterson, Dr. Ricardo Carrion and their research team announced the development of the common marmoset monkey as a research model for Lassa fever, a potential biological weapon that causes natural disease outbreaks and kills several thousand people each year in West Africa. An advantage of the marmoset, a small primate that weighs about one pound when fully grown, is that its small size makes it much easier for scientists to study in a laboratory setting. SFBR investigations found that the marmoset’s response to Lassa infection completely mimics the response in people who

develop symptoms, making it a viable research model that is expected to speed the testing of numerous candidate vaccines and drug therapies. With success in developing this animal model for Lassa fever studies, SFBR virologists are now conducting studies to determine the efficacy of this animal model for research on Ebola and Marburg viruses.

On a similar front, SFBR scientists were awarded a \$1.5 million contract by the Department of Homeland Security in 2007 to implement one of the most comprehensive research programs to date on the Marburg virus. The 18-month contract is aimed at exploring how the Marburg virus causes disease in order to shed light on ways scientists might defeat it with a drug therapy or vaccine.

Tracking the spread and increasing severity of emerging diseases

For years, Dr. Rebeca Rico-Hesse has kept her eye on dengue, a mosquito-borne virus that in its mild form causes intense flu-like symptoms and in its severest form causes hemorrhagic fever. Through a variety of epidemiological studies and laboratory investigations, she has tracked the spread of this disease around the globe as she also has tried to find ways to defeat it. Current therapies are limited to rest and the consumption of fluids, while prevention methods are limited to attempts to eradicate the type of mosquito that can carry dengue, or at least lessen people's exposure to it.

In the 1990s, she showed for the first time that the severe form of dengue can be contracted not only after infection with more than one of its milder strains, but also from a single infection with the more virulent strain. Therefore, when dengue hemorrhagic fever was diagnosed in the Texas border city of Brownsville in 2005, she and her research team were called upon to help determine the cause. Their investigation led to the genetic identification of the culpable virus and confirmed that the more virulent form of dengue is now being transmitted along the Texas-Mexico border. In 2007, that unfortunate but major finding was published in what has quickly become a highly cited paper in the journal *Clinical Infectious Diseases*.

Dr. Rico-Hesse also is making continued advances in the effort to find effective anti-viral drugs or vaccines against dengue. In 2006, she published a paper on her success in developing the first animal model for dengue research: an immuno-suppressed mouse transplanted with human cord blood cells to give it a humanized immune system, enabling efficacy tests of anti-viral medications to treat dengue. In 2007, the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation awarded a philanthropic grant to Dr. Rico-Hesse to further develop this valuable animal model so that it can be used for vaccine studies.

Because of her outstanding work, Dr. Rico-Hesse has been asked to co-chair a workshop at the National Institutes of Health to develop a plan to expand and obtain specific, broader funding for these research models. She also has been invited to chair a symposium and present research results at the Second International Conference on Dengue and Dengue Hemorrhagic Fever in Thailand in October 2008.



SFBR plays an increasingly important role in the battle against the AIDS pandemic

Every day, more than 6,800 people become infected with HIV, and over 5,700 die from AIDS, mostly because of inadequate access to HIV prevention and treatment services, according to the 2007 AIDS Epidemic Update published by the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO). That translates to an estimated 33.2 million people living with HIV worldwide, and 2.5 million people newly infected with HIV in 2007. Thus, the “HIV pandemic remains the most serious of infectious disease challenges to public health,” the report states.

While Sub-Saharan Africa has been hardest hit – AIDS remains the leading cause of death in that region – the United States is reported by UNAIDS and WHO to be one of the countries with the largest number of HIV infections in the world. Fortunately, advances in and access to life-prolonging medications have enabled more people to live with the disease in the more affluent countries of North America and Western and Central Europe. On the flip side, as more people live with the disease for a longer time, new infection rates can continue to climb, a trend that’s been seen in Europe over the last five years.

For First World and Third World countries alike, then, the elusive AIDS vaccine remains a coveted prize. But the quest for such a vaccine has been unlike any other, mostly because HIV does not respond to traditional vaccination methods in the same way as other viruses. In fact, the principal human clinical trials in AIDS prevention – two involving candidate vaccines and two with microbicides – have recently failed. Results indicated that attempts to prime the immune system to fight off an HIV infection actually increased susceptibility to infection.

For this reason, the National Institutes of Health asked AIDS researchers to take a fresh look at HIV and AIDS prevention and search for entirely new approaches. For these efforts, the already valuable nonhuman primate models for AIDS research will play an increasingly vital role in understanding HIV infection in humans and predicting the human response to vaccines and other prevention methods. In fact, work at SFBR is already lending some key insights.

African monkeys offer insight on a better vaccine design

Dr. Jonathan Allan, a scientist in the SFBR Department of Virology and Immunology and a core scientist with the Southwest National Primate Research Center, studies the basic process of AIDS by examining simian immunodeficiency viruses in their natural host, the





African green monkey. A key feature of infection of African nonhuman primate hosts is their remarkable resistance to disease.

They live with the virus without getting sick.

Dr. Allan's laboratory has reported several important findings that essentially show that these monkeys do not limit virus replication. High levels of the virus are seen in their system, yet what seems to help protect them is counterintuitive. Their immune response to infection is actually less robust than a host who succumbs to disease.

What does that mean? To put this in context, the recent HIV vaccine failure reported by Merck was due in part to the fact the vehicle used to deliver and express HIV genes was itself fueling the fire by stimulating greater numbers of susceptible reactive immune cells called T cells, leading to a greater number of targets for the virus to replicate. In contrast, African monkeys resist disease in part because they blunt their response, producing less chronic inflammation. It is precisely that inflammation which is now thought to promote the slow decline of T cells, which results in AIDS.

One of the overall strategies being re-examined by vaccinologists is to look more carefully at antibody responses that can neutralize or prevent new infections. Dr. Allan's studies have recently focused on a close examination of virus-specific neutralizing antibodies in the natural hosts. He and his research team have found that there are indeed highly conserved regions of the virus that, under the right circumstances, could be used as targets for a new vaccine design. Their future efforts are directed toward a better understanding of these novel antibody responses, which could one day be used in an effective vaccine for AIDS.

An "outside-the-box approach" to HIV vaccination and treatment

Already moving ahead and finding signs of success with an "outside-the-box approach" to defeating HIV is Dr. Krishna Murthy, a scientist in the Department of Virology and Immunology and a core scientist with the

Southwest National Primate Research Center. He is part of an NIH-funded team headed by New York-based United Biomedical that has been developing and testing a vaccine designed to induce the production of antibodies that bind with the CD4 receptor complex, which is used by HIV to enter and infect immune cells. By binding with that receptor complex, the antibody blocks an essential mechanism that all subtypes of HIV need to infect a cell – and if the virus cannot infect a cell, it eventually dies. If successful, this approach could theoretically be used both to prevent and treat infections with all sub-types of HIV, a feat that has long seemed nearly impossible.

Preliminary studies in both guinea pigs and baboons have been very encouraging. In these animals, the peptide-based vaccine elicited the proper immune response, leading to the production of the type of antibodies needed to bind with the CD4 receptor complex on immune cells. Now additional safety and immunogenicity studies in baboons are underway to determine the appropriate dose, adjuvant formulation, and frequency of the vaccination regimen to induce the optimal immune response. Once the baboon studies are completed, Dr. Murthy and his colleagues plan to do a proof-of-concept study in chimpanzees, which will be immunized with the vaccine and then challenged with a primary isolate of HIV to determine vaccine efficacy and immune correlates of protection.

Protecting neonates from the transmission of the AIDS virus

Since moving to SFBR from Harvard in 2006, Dr. Marie-Claire Gauduin has been establishing a successful pediatric AIDS research program using the rhesus macaque model of simian immunodeficiency virus (SIV). In a pilot study funded by the Southwest National Primate Research Center in 2007, Dr. Gauduin used SIV as a tool to determine which differences between immature and mature immune systems are responsible for the increased susceptibility of neonates to SIV/HIV infection. This interesting research project has recently shown that newborn monkeys infected with a less pathogenic form of SIV can control infection even in the absence of antiviral treatment, suggesting that, with infected human infants, treatment may be quite successful in rescuing or preserving the child's immune response.

Among other exciting efforts, Dr. Gauduin has





entered a new collaboration with Dr. Susan Zolla-Pazner from the VA Hospital-New York University looking at passively transferred anti-SHIV monoclonal antibodies to protect newborns from the transfer of infection from their mothers.

Development of valuable new research methods

Another major advance in the study of AIDS and other infectious diseases has been the use of a “tether” technology for the intensive study of acute SIV infection and other viral infections. Infection of rhesus macaques with SIV is the preferred animal model for the development and testing of HIV vaccines; animals protected from SIV challenge by live attenuated vaccines are an invaluable tool for determining immune correlates of protection. The acute phase of SIV infection, in which immune responses are most critical for slowing disease progression, occurs within the first four weeks of exposure. The small window of time available for observing critical immune responses makes obtaining adequate blood samples with sufficient frequency difficult.

Dr. Luis Giavedoni, a scientist with the SFBR Department of Virology and Immunology and a core scientist with the Southwest National Primate Research Center, was the first to apply a previously reported nonhuman primate tether system to study viral immunology. The use of the tether technology allowed for frequent blood sampling without using restraints or sedation, thereby reducing the potentially confounding physiological changes induced by stress. These data indicated the validity of using the tether system for evaluation of acute phase anti-SIV responses. Similarly, this technology can be applied to the study of immune responses in other viral infections in which frequent sampling in small windows of time would be useful.

Ingenious efforts to prevent or repair disorders of the nervous system

Diseases and other ailments affecting the nervous system can be among the most difficult to endure, as a breakdown in the highly complicated network of the brain, spinal cord, nerves, muscles and other nervous system components can destroy our senses, thought processes, movements, and any unlearned reflex of the body. The genetic and environmental factors that can cause nervous system disorders may be as diverse or even more so than the diseases' effects, which is why research efforts in this area require multidisciplinary approaches.

Defending against "nervous" viruses

At SFBR, Dr. Anthony Griffiths focuses his efforts on a virus that infects the nervous system. Herpes B virus (BV), which can be found naturally in macaque monkeys, remains fairly benign in its natural host and mostly causes cold-sore-like lesions. However, when it is transmitted to humans, the contrast in its effects is dramatic, as it leads to encephalitis and is almost always fatal. For this reason, herpes B virus may only be studied in a BSL-4 laboratory like the one at SFBR.

Genetically, BV is very similar to herpes simplex virus (HSV), which in humans tends to remain benign, causing cold sores. However, it can turn more serious, and in fact is the most common viral cause of encephalitis.

Therefore, one of Dr. Griffiths' aims with his research on herpes B is to shed light on how herpes simplex virus causes encephalitis, and subsequently, on novel therapeutic targets for herpes simplex virus infections.

In collaboration with Dr. Xiu-Jie Wang at the Chinese Academy of Sciences, and with the support of a pilot study grant funded by the Southwest Foundation



Forum, Dr. Griffiths has been studying a new class of molecules called microRNAs, which are important regulators of gene expression. He and his collaborators have discovered several BV-encoded microRNAs, and based on their computational analyses, the researchers have determined that these microRNAs are highly likely to regulate certain viral genes. Interestingly, these genes have been predicted by others to be important for the remarkable neurological disease caused by herpes B virus. Now, Dr. Griffiths and his colleagues aim to study these genes, along with the proteins they encode, to determine their roles in the virus' biology and the disease it causes. They anticipate that these studies will uncover novel therapeutic targets, not just for BV, but also for other neuropathogenic viruses.

Demystifying age-associated disorders of the nervous system

Sometimes nervous system problems can occur simply as a result of aging. For example, it is a well documented phenomenon that people's sense of thirst declines with age. That is believed to be a major factor in the increased risk of dehydration among the elderly, since when we don't feel thirsty, we tend to drink less water and other fluids.

At SFBR, Dr. Robert Shade in the Department of Physiology and Medicine is collaborating on a study to help determine what changes in the brain might be responsible for this declining sense of thirst. Study results published by the group in December 2007 in the *Proceedings of the National Academy of Sciences of the United States of America* point to one region in particular: the anterior mid-cingulate cortex.

Researchers arrived at this conclusion after examining PET scans of study volunteers at various levels of thirst and satiation, along with the subjects' answers to survey questions about how thirsty they felt at the time.

What they found was that healthy subjects in their 20s and healthy

subjects in their 60s and 70s were equally thirsty after an IV infusion with a saline solution. In both groups, the same section of the brain “lit up” on the PET scan. However, when they were allowed to drink as much as they wanted in response to that thirst, the older research subjects drank less water, stopping at a point where they no longer felt thirsty, but they still were not properly hydrated. Subsequent PET scans were again the same for both groups, indicating that the thirst signal in the anterior mid-cingulate cortex was “turned off” prematurely in the older adults.

While researchers do not yet have the answer as to why this is, they have theories to pursue, and more importantly, they know which area of the brain needs to be the focus of further study. They will now pursue a more detailed investigation in mice and try to find the physiological mechanisms that lead to these results. With those details, they believe it may be possible to devise a therapy or a drug to reverse the effect and restore a proper sense of thirst in the elderly.

This study is funded through a grant from the G. Harold and Leila Y. Mathers Charitable Foundation in New York to the Howard Florey Institute of the University of Melbourne, Australia. In addition to the Florey Institute and SFBR, other collaborators include the Baker Research Institute in Australia and the University of Texas Health Science Center at San Antonio.

New approaches to other brain-associated disorders

Although it is our most vital organ, surprisingly little is known about what constitutes a “normal” brain. That makes it harder to uncover what has gone awry in people suffering from mental illness and other brain-associated disorders, and ultimately, it often leaves physicians treating symptoms rather than causes of conditions such as Alzheimer’s and Parkinson’s disease, schizophrenia, and many other ailments.

That is why Dr. John Blangero, a geneticist at SFBR, and Dr. David Glahn, a psychologist and associate professor at the University of Texas Health Science Center at San Antonio, teamed up in 2007 to initiate the largest study of its kind to map out normal variations in brain structure and function and identify the genes responsible for those variations. The five-year investigation, funded by two cooperative NIH grants totaling \$7 million, involves 1,000 members of the SFBR-sponsored San Antonio Family Heart Study, on whom demographic and health information, blood samples and genetic data have been maintained for more than 15 years. These participants are now being recalled to undergo a series of cognitive tests and high-resolution MRIs at UTHSCSA. Afterwards, Dr. Glahn’s group analyzes the cognitive information and brain images to sort out data relevant for Dr. Blangero’s group to search for genes related to normal brain variations.

The scientists’ findings are expected to reveal a tremendous amount of information about basic brain biology, normal variation in brain structure and function, and the genes that influence that normal variation. In the process, that knowledge will better inform other investigations searching for explanations and treatments for the root causes of brain disorders rather than just the symptoms.

In a parallel study, Dr. Jeff Rogers at SFBR is collaborating with researchers at UTHSCSA on a study looking at brain structure and function in baboons. In 2007, analyses of the brain





structure obtained from MRIs in combination with baboon pedigree information revealed high heritabilities for brain structure, with 82 percent of variation in brain volume being attributable to genetic factors.

And in separate efforts looking at measurable traits of brain structure and function that are correlates of psychiatric disease, Dr. Laura Almasy is searching for genetic influences on susceptibility to alcoholism and schizophrenia. She collaborates on the Collaborative Study on the Genetics of Alcoholism (COGA), a major multi-

institutional research project that in 2007 reported the discovery of a novel gene associated with susceptibility to alcoholism. In a separate study searching for genes that influence schizophrenia and psychosis, Dr. Almasy and Dr. Michael Escamilla at UTHSCSA found evidence for linkage of schizophrenia to regions on chromosomes 1, 5, and 18. Localization of genes is the first step toward gene identification, which in turn leads to knowledge of biological pathways that may be targeted for intervention and treatment.

Developing the baboon model of epilepsy

Epilepsy is a neurological disorder that affects about 50 million people throughout the world, and animals at SFBR might offer one of the best research models for studying it. Why? While less than 1 percent of the U.S. population suffers from epilepsy, in which seizures are recurring, and more than 5 percent of the U.S. population has had at least one seizure, scientists studying wild red baboons in the late 1960s and early 1970s found the natural occurrence of spontaneous seizures in anywhere from 40 to 100 percent of sample groups, making the baboon the nonhuman primate species most susceptible to the disorder. And it's not just the red baboon. Other subspecies of baboons, including the olive and yellow baboons that make up the majority of the pedigreed colony at the Southwest National Primate Research Center, also have naturally occurring epilepsy.

Although baboons' unique susceptibility to epilepsy and spontaneous seizures has long made them the focus of clinical research on epilepsy, no one has studied these animals to search for genes that play a role in the disorder. Seeing the tremendous potential to find genes that influence epilepsy in baboons and then apply that knowledge to help improve diagnosis and treatment in humans, Dr. Jeff Williams of the Department of Genetics has been working to develop the baboon as a natural animal model for investigations on the genetics of epilepsy.

In 2007, in collaboration with Dr. C. Akos Szabo at the University of Texas Health Science Center at San Antonio, Dr. Williams published novel results validating the SNPRC pedigreed baboons as animal models for human epilepsy. They demonstrated that the diagnostic imaging techniques currently used for investigating human epilepsy could be applied in baboons. Through PET imaging of the brains of six epileptic baboons and four non-epileptic baboons, Drs. Williams and Szabo demonstrated that the same electrical and chemical signals observed in human epileptics are seen in baboons. This valuable study paves the way for the future development of the baboon in intensive studies of epilepsy as well as in more general neuroimaging studies.

Extraordinary resources support a wide scope of national research efforts on human health and disease

SFBR is home to several extraordinary resources that enable or greatly enhance SFBR scientists' ability to conduct cutting-edge science and attract national collaborations on a wide range of research initiatives.

For example, the state-of-the-art laboratories in the Department of Virology and Immunology, which include several BSL-3 laboratories and the nation's only privately owned BSL-4 laboratory, have allowed the Foundation to excel in the area of infectious disease and biodefense research, as can be seen by many of the notable discoveries described in this report.

Likewise, the world's largest computing cluster for genetic research on human disease, developed by SFBR scientists and housed in the Foundation's AT&T Genomics Computing Center, has dramatically enhanced the speed with which SFBR scientists can search for disease-influencing genes. Coupled with the scientific know-how of SFBR's stellar genetics team and tremendous advances in the Foundation's molecular research capabilities, it allows SFBR scientists to embark on ambitious research projects that would not be feasible at other institutions. The fruits of those efforts, too, are outlined in various sections of this annual report.

Nearly impossible to report in detail is the far-reaching impact of the Foundation's Southwest National Primate Research Center. As one of only eight National Primate Research Centers funded by the National Institutes of Health to facilitate critical biomedical research efforts that require primate models of human disease, the SNPRC is a vital national resource that serves scientists at major research institutions across the country.

The value of nonhuman primates to national research

As the animals most similar to humans in genetics and physiology, nonhuman primate models are the gold standard for biomedical research that requires the use of animals. In fact, many research programs can only be conducted successfully using nonhuman primates, since no other animals so completely share the complex physiological and disease-related processes that are critical to understanding the pathogenesis of complex and infectious diseases. The close relationship between humans and nonhuman primates also means that genes found to be important for determining differential susceptibility to disease in monkeys will also have significant effects in humans.

Just as some of the best biomedical research relies on nonhuman primates, some of the best nonhuman primate research in the country relies on the specialized resources of the SNPRC.

Among the nearly 4,000 animals at the SNPRC, the center houses the largest baboon colony in the world, including a unique colony of pedigreed animals for genetic research on





a broad range of chronic diseases and physiological traits. The chimpanzee colony at the SNPRC also is one of the largest available to researchers and is highly utilized for hepatitis and AIDS research, as well as for developing novel therapeutics for both infectious and noninfectious human diseases. Growing colonies of rhesus monkeys and marmosets are also helping to meet national demand for nonhuman primate models needed for research on AIDS, pharmacology, aging studies, biodefense research, and a wide variety of other human health efforts. Almost all of the primates used at the SNPRC are produced in breeding colonies there.

Research collaborations span the country, range of human health issues

Access to these outstanding animal research resources, along with the skills and expertise of SNPRC veterinary staff and core scientists – who offer specialized consultation in the areas of genomics; infectious diseases and biodefense; development and aging; and chronic diseases – are highly sought by scientists around the country. The high demand for SNPRC consultation and professional services is evident in the number and breadth of research projects underway at the center.

The 65 ongoing research projects at the SNPRC cover the full gamut of human health issues, including atherosclerosis, hypertension, obesity, diabetes, metabolic syndrome, osteoporosis, lumbar disc degeneration, epilepsy, sickle cell anemia, non-Hodgkin's lymphoma, behavioral and psychiatric disorders, prenatal and neonatal disease, aging, tuberculosis, Lassa fever, West Nile fever, equine encephalitis, pneumonia, influenza, periodontitis, hepatitis B and C, AIDS, and biodefense.

In these laudable endeavors, the SNPRC is providing research support to over 200 investigators, 75 percent of whom are located at institutions other than SFBR. Collaborators include investigators at major biomedical research institutions within Texas, such as Baylor College of Medicine, the University of Texas at Austin, the University of Texas Medical Branch at Galveston, the University of Texas Southwestern Medical School, and the University of Texas Health Science Center at San Antonio, as well as other top research institutions throughout the country, including the Scripps Clinic, the Salk Institute, Harvard Children's Hospital, Johns Hopkins University, and the University of California, San Francisco.

Advancing nonhuman primate genetics

In a true national collaboration with far-reaching impact, SFBR and the SNPRC supported efforts that led to the publishing of the genetic sequence of the rhesus monkey, the most widely used nonhuman primate in research on human health and disease. Following extensive efforts by a multi-center team funded by the National Human Genome Research Institute, the genetic sequence of the rhesus genome was published in *Science* on April 13, 2007. Work on the sequence was conducted at the Baylor College of Medicine Human Genome Sequencing Center in Houston, the Genome Sequencing Center at Washington University in St. Louis, and the J. Craig Venter Institute in Rockville, Md., under the direction of Dr. Richard Gibbs, director of the BCM-HGSC.

The consortium had assistance in this effort from Dr. Jeff Rogers, a geneticist at SFBR and core scientist with the SNPRC and a co-author on the publication in *Science*. Dr. Rogers was the lead author on a white paper that nominated this species as the second nonhuman primate to be selected by the NHGRI for sequencing, after the chimpanzee. Once the rhesus sequencing project was approved, Dr. Rogers served as a liaison between the genome sequencing centers and primatology centers. Other valuable assistance also came from the SNPRC, as the DNA sequence was derived from a female rhesus macaque monkey that was part of an SNPRC colony.

Around the world, the rhesus monkey is the primary model for the study of AIDS as well as for research in neuroscience. It also is a vital animal model for research on metabolic disorders such as cardiovascular disease, diabetes and obesity; reproductive biology; aging; vision; mental health and addictive disorders; pharmacology; and a host of other human diseases. With the breadth of research initiatives that involve the rhesus and the monkey's closeness to humans in genetics and physiology, this genome sequencing is expected to have a quick and dramatic impact on biomedical research.





New initiatives

With the addition of new personnel and research collaborations, new approaches to disease amelioration, and the application of new technologies, the SNPRC has recently taken some major leaps forward into new areas of biomedical research. Stem cell biology and gene therapy, for example, are two new conceptual areas that have begun to take shape at the Primate Center.

There is great hope in the potential of both adult and embryonic stem cells to treat a wide array of human health problems. However, with embryonic stem cell research still in its infancy, and with additional ethical concerns surrounding this area of research in humans, most embryonic stem cell research to date has been done in mice. So the big question that remains is, “Will these methods work, and will they work safely, in humans?”

With its baboon colony, the SNPRC is perfectly positioned, both scientifically and ethically, to help bridge this important concept. Led by Dr. Gerald Schatten of the University of Pittsburgh, with on-site direction by Dr. Cal Simerly, an exciting new effort is underway to develop stable baboon embryonic stem cells and to test the safety of these technologies. Already, the first embryonic stem cell line from a baboon has been established at the SNPRC. Since human stem cells contain the powerful potential for treating a variety of diseases such as diabetes, heart disease, and crippling neurological diseases such as Parkinson’s and Alzheimer’s, the scientific community is looking forward to results of tests with such new stem cell reagents in nonhuman primate models.

Another exciting area under intense investigation is gene therapy. As one of the SNPRC’s external collaborators at Baylor College of Medicine, Dr. Larry Chan has been studying the potential of using genetically engineered viral vectors to “transform” small subsets of liver cells within monkeys into insulin-producing cells. In theory, this type of therapy would eliminate the need for a diabetic patient to administer insulin on a daily basis. The ongoing experiments at the SNPRC are designed to determine the safety of such an approach.

As more and more emphasis is placed on human translational research – taking research from the laboratory bench to human clinical trials – the SNPRC is in a unique place at this crossroads of research emphasis. Its role in national research efforts is expected only to increase, further fulfilling SFBR’s mission of advancing the health of our global community through innovative biomedical research.

New Grants and Contracts Awarded in 2007

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant

Total Amount to SFBR

Federal Research Grants and Contracts

National Institutes of Health

Maintenance and Operation of a Chemical Synthesis Facility
(Dr. Pemmaraju N. Rao), 5 Years

\$ 3,653,101

National Institutes of Health

Copy Number Variation in Malaria Parasite (Dr. Timothy J.C. Anderson), 5 Years

\$ 2,070,949

National Institutes of Health

Establishment of an SPF Rhesus Macaque Colony (Dr. Larry B. Cummins), 5 Years

\$ 1,850,763

National Institutes of Health

Genetic Analysis of Idiopathic Thrombosis (Dr. Laura Almasy), 4 Years

\$ 1,847,435

National Institutes of Health

Identification of Regulatory Variants in Novel Candidate Genes for Diabetes
(Dr. Joanne E. Curran), 5 Years

\$ 1,736,478

National Institutes of Health/University of Texas Health Science Center at San Antonio

Nutrient Restriction: Placental and Fetal Brain and Renal Outcomes and Mechanisms
(Dr. Laura A. Cox), 5 Years

\$ 1,655,181

Department of Homeland Security

Filovirus Major Gap Studies (Dr. Jean L. Patterson), 2 Years

\$ 1,495,255

National Institutes of Health/University of Texas Health Science Center at San Antonio

Nutrient Restriction: Placental and Fetal Brain and Renal Outcomes and Mechanisms
(Dr. Karen Rice), 5 Years

\$ 1,484,000

Defense Threat Reduction Agency/Stanford Research Institute

Accelerated Path to Safe and Effective Therapeutics (APSET)
(Dr. Ricardo Carrion Jr.), 2 Years

\$ 1,254,809

National Institutes of Health

Supplement to SNPRC Base Grant – (Mr. John C. Kerr), 8 Months

\$ 959,659

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant

Total Amount to SFBR

<i>National Institutes of Health/Scripps Research Institute</i> Immunotherapeutics vs Ebola Sudan: Development, Structural and Functional Analysis (Dr. Jean L. Patterson), 4 Years	\$ 921,510
<i>National Institutes of Health/Brown University</i> Genetics of Reproductive Senescence (Dr. John Blangero), 5 Years	\$ 834,451
<i>National Institutes of Health/Magee Womens Research Institute & Foundation</i> Pluripotent Stem Cells in Development and Disease (Dr. Karen Rice), 1 Year	\$ 728,115
<i>National Science Foundation</i> Human Origins: Genetic and Molecular Basis of Craniofacial Evolution (Dr. Jeff Rogers), 5 Years	\$ 705,456
<i>National Institutes of Health/Baylor College of Medicine</i> Aerosol Delivery of HDAd into Primate Lungs: Preclinical CF Gene Therapy Studies (Dr. Karen Rice), 4 Years	\$ 695,142
<i>Defense Threat Reduction Agency</i> Novel Diagnostics for Botulinum Toxins (Dr. Andrew Hayhurst), 3 Years	\$ 593,150
<i>National Institutes of Health/Wright State University</i> The Genetics of Infant Growth and Later Obesity (Dr. John Blangero), 5 Years	\$ 544,849
<i>National Institutes of Health/Medical College of Wisconsin</i> Candidate Genes Affecting Adolescent Metabolic Syndrome (Dr. John Blangero), 5 Years	\$ 515,722
<i>National Institutes of Health</i> A Linkage Map for <i>Schistosoma mansoni</i> (Dr. Timothy J.C. Anderson), 2 Years	\$ 470,250
<i>National Institutes of Health</i> Resolution of Acute Hepatitis B Virus Infections in Chimpanzees (Dr. Robert E. Lanford), 2 Years	\$ 448,519
<i>National Institutes of Health</i> A Baboon Model for the Genetics of Cortical Bone Material Properties (Dr. Lorena M. Havill), 2 Years	\$ 377,010
<i>National Institutes of Health/University of Texas Health Science Center at San Antonio</i> Type 2 Diabetes Gene Discovery Linked to 3P in Hispanics (Dr. Harald H.H. Göring), 5 Years	\$ 231,609
<i>National Institutes of Health/University of Texas Health Science Center at San Antonio</i> The Common Marmoset as a Primate Model of Maternal Obesity (Dr. Kathleen M. Brasky), 4 Years	\$ 217,209
<i>Naval Research Laboratories</i> Development and Testing of Recombinant Single Domain Antibodies (Dr. Andrew Hayhurst), 1 Year	\$ 175,000
<i>National Institutes of Health/University of Texas Medical Branch at Galveston</i> Regional VI Center for Biodefense and Emerging Infections New Opportunities Supplement: Preclinical Testing of YF17D/LAS, a Bivalent Attenuated Vaccine for Lassa and Yellow Fevers (Dr. Jean L. Patterson), 1 Year	\$ 160,087

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Continued

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant

Total Amount to SFBR

<i>National Institutes of Health/SIGA Technologies</i> Antiviral Drugs for Lassa Fever Virus (Dr. Ricardo Carrion Jr.), 1 Year	\$ 142,997
<i>National Institutes of Health/Oregon Health & Science University</i> Molecular Phenotypes of Primary Open Angle Glaucoma (Dr. Jac Charlesworth), 5 Years	\$ 119,364
Miscellaneous federal research grants and contracts (under \$100,000 each)	\$ 884,480
TOTAL FEDERAL RESEARCH GRANTS AND CONTRACTS	\$ 26,772,550

Commercial and Other Non-Federal Research Grants and Contracts

Commercial Research Grants and Contracts	\$ 2,698,523
Miscellaneous Research Grants and Contracts	\$ 227,669
TOTAL COMMERCIAL, OTHER NON-FEDERAL RESEARCH GRANTS AND CONTRACTS	\$ 2,926,192

Philanthropic Research Grants

<i>G. Harold and Leila Y. Mathers Charitable Foundation</i> Research in Brain Function (Dr. Derek Denton, Florey Institute, principal investigator; Dr. Robert E. Shade, SFBR, co-investigator), 3 Years	\$ 1,050,000
<i>Richard & Dianne Azar</i> Genetic Dissection of Cystinosis: An Innovative Program for Novel Mechanism/Gene Discovery (Dr. John Blangero), 1 Year	\$ 588,344
<i>Robert J. Kleberg Jr. and Helen C. Kleberg Foundation</i> Monodelphis Research Program (Dr. John L. VandeBerg), 1 Year	\$ 396,456
<i>Robert J. Kleberg Jr. and Helen C. Kleberg Foundation</i> Development of a Mouse Model of Dengue Hemorrhagic Fever (Dr. Rebeca Rico-Hesse), 1 Year	\$ 111,344
<i>George W. Brackenridge Foundation</i> Postdoctoral Fellowship Funding (Dr. J. Michael Proffitt), 2 Years	\$ 110,000
<i>The Dr. Robert C. and Veronica Atkins Foundation</i> Effect of Visceral Fat on Insulin Sensistivity (Dr. Raul A. Bastarrachea), 1 Year	\$ 100,000
<i>Kronkosky Charitable Foundation</i> Identification of Novel Candidate Genes Predicting Diabetes Development (Dr. Joanne E. Curran), 1 Year	\$ 100,000

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant	Total Amount to SFBR
<i>Kronkosky Charitable Foundation</i> Investigation of miRNA Gene Regulation in the Metabolic Syndrome (Dr. John Blangero), 1 Year	\$ 100,000
<i>H-E-B Tournament of Champions</i> GEMM Program (Dr. Anthony Comuzzie), 1 Year	\$ 65,000
<i>Morrison Trust</i> Protein Biomarkers for Early Detection of Liver Cancer (Dr. Robert E. Lanford), 1 Year	\$ 60,211
<i>Max and Minnie Tomerlin Voelcker Fund</i> Endothelial Progenitor Cells Mobilized by Arterial Injury (Dr. Qiang Shi), 1 Year	\$ 50,000
<i>Max and Minnie Tomerlin Voelcker Fund</i> Defining High Risk Heart Disease Genomic Profiles for Potential Interventions (Dr. Laura A. Cox), 1 Year	\$ 49,994
<i>Kronkosky Charitable Foundation</i> Effects of Brain Glucose-Dependent Insulinotropic Polypeptide (GIP) Signaling on Glucose Metabolism in a Non-Human Primate (Dr. Robert E. Shade), 1 Year	\$ 49,903
<i>Max and Minnie Tomerlin Voelcker Fund</i> Identification of Novel Genes Involved in Chemotherapeutic Toxicity (Dr. John Blangero), 1 Year	\$ 49,835
<i>Max and Minnie Tomerlin Voelcker Fund</i> Genetics of Homocysteine and its Correlation with Cardiovascular and Gallbladder Diseases in Mexican Americans (Dr. Vidya S. Farook), 1 Year	\$ 49,824
<i>Max and Minnie Tomerlin Voelcker Fund</i> Creation of Immortalized Chimpanzee and Baboon Hepatocyte Cell Lines for Analysis of HCV Associated Disease and Liver Cancer (Dr. Robert E. Lanford), 1 Year	\$ 48,121
<i>Max and Minnie Tomerlin Voelcker Fund</i> The Discovery of New Drugs for the Treatment of Cancer (Dr. Susan L. Mooberry), 1 Year	\$ 47,873
<i>Fondazione Telethon</i> Gene Therapy Using Adeno-Associated Vectors in Baboons (Dr. Karen Rice), 1 Year	\$ 39,482
<i>Max and Minnie Tomerlin Voelcker Fund</i> Development of a Drug Delivery System to Investigate Mechanisms of Herpes Simplex Virus Drug Resistance Using a Mouse Eye Model of Infection (Dr. Anthony Griffiths), 1 Year	\$ 39,318
<i>American Society for Bone and Mineral Research</i> Identifying Genetic Determinants of Bone Metabolism Using Transcriptional Profiles (Dr. Lorena M. Havill), 1 Year	\$ 38,500

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Continued

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant

Total Amount to SFBR

Max and Minnie Tomerlin Voelcker Fund

Development of a Non-Human Primate Model of Diet Induced Obesity
(Dr. Raul A. Bastarrachea), 1 Year

\$ 37,200

Gates Malaria Partnership

Molecular Evidence of Drug Selection in *Plasmodium falciparum* Malaria
(Dr. Standwell C. Nkhoma, visiting scientist, principal investigator;
Dr. Timothy J.C. Anderson, SFBR collaborator), 1 Year

\$ 35,000

Semp Russ Foundation of the San Antonio Area Foundation

Role of Chromosome 11 in Blood Pressure Variation (Dr. Sue Rutherford), 1 Year

\$ 34,969

Semp Russ Foundation of the San Antonio Area Foundation

Rapid Identification of Genetic Variation Influencing Obesity Using the
San Antonio Family Heart Study (Dr. Jac Charlesworth), 1 Year

\$ 34,927

Joe and Jessie Crump Foundation

Cancer Drug Development (Dr. Susan L. Mooberry), 1 Year

\$ 30,000

Semp Russ Foundation of the San Antonio Area Foundation

Characterization of a Positional Candidate Gene for Mitochondrial DNA Copy Number
(Dr. J. Michael Proffitt), 1 Year

\$ 26,180

Joe and Jessie Crump Foundation

Battling Cancer with Tumor Targeting Salmonella Bacteria (Dr. Andrew Hayhurst), 1 Year

\$ 25,000

Southwest Foundation Forum

Contribution of Carboxylesterase Variants to Heart Disease Risk (Dr. Laura A. Cox), 1 Year

\$ 25,000

Southwest Foundation Forum

Direct Identification of Drug Resistance Mutations in Malaria Parasites
(Dr. Timothy J.C. Anderson), 1 Year

\$ 25,000

Southwest Foundation Forum

Development of the Baboon as a Model for PSA Biology Studies (Dr. James Mubiru), 1 Year

\$ 25,000

Southwest Foundation Forum

Investigating Chromosome 11 micro RNA Transcripts for Involvement in Change
in Blood Pressure over Time in Mexican Americans of the San Antonio Family
Heart Study (Dr. Sue Rutherford), 1 Year

\$ 24,972

Southwest Foundation Forum

Rapid Identification of Genetic Variation Influencing Total Antioxidant Status
(Dr. Jac Charlesworth), 1 Year

\$ 24,960

Southwest Foundation Forum

A Texan Cure for Malaria (Dr. Susan L. Mooberry), 1 Year

\$ 24,935

Grant Sponsor, Title, SFBR Principal Investigator, Length of Grant	Total Amount to SFBR
Southwest Foundation Forum Whole Genome Transcriptional Profiling of Cysteamine-Treated Human Cystinotic Cell Lines (Dr. Katy Freed), 1 Year	\$ 24,676
NAASO - The Obesity Society Effect of High Fructose Meal on Gene Expression of Appetite-Related Peptides in Baboons (Dr. Venkata Saroja Voruganti), 1 Year	\$ 24,416
Southwest Foundation Forum Proteomic Characterization of Anthrax Infection in Cynomolgus Macaques (<i>Macaca fascicularis</i>) (Dr. E. Ellen Schwegler), 1 Year	\$ 24,409
Southwest Foundation Forum Identifying Osteoporosis Genes Through Transcriptional Profiling (Dr. Lorena M. Havill), 1 Year	\$ 23,971
Southwest Foundation Forum Characterization of Normal Variation in Cytokines Associated with T-Helper Cell Subset Effects on Atherosclerosis in Healthy Baboons (Dr. Amanda Vinson), 1 Year	\$ 23,825
Shelby Rae Tengg Foundation Preclinical Evaluation of New Antimitotics (Dr. Susan L. Mooberry), 1 Year	\$ 7,500
TOTAL PHILANTHROPIC RESEARCH GRANTS*	\$ 3,646,145
TOTAL RESEARCH GRANTS AND CONTRACTS AWARDED IN 2007	\$ 33,344,886

Construction and Renovation Grants

National Institutes of Health Improvement of Nonhuman Primate Housing Facilities (Dr. John L. VandeBerg), 1 Year	\$ 174,806
TOTAL CONSTRUCTION AND RENOVATION GRANTS	\$ 174,806
TOTAL GRANTS AND CONTRACTS AWARDED TO SFBR IN 2007	\$ 33,519,692

*Additional philanthropic grants were awarded in 2007 for the purchase of scientific equipment. The granting institutions and their gift amounts are as follows:

Granting Organization	Total Amount to SFBR
AT&T Foundation	\$ 1,000,000
Elizabeth Huth Coates Charitable Foundation	\$ 300,000
The Zachry Foundation	\$ 50,000
The Edouard Foundation	\$ 26,000

Why Support SFBR?

It's a **fact of life** that grants and other income do not provide all the resources SFBR needs to achieve its important mission. Since the organization's founding, giving has played the role of a powerful enabler of progress, making philanthropy one of the cornerstones of this institution. Here are a few examples of how your financial support can make all the difference to SFBR scientists:

- ▷ **Leverage.** On average, for every \$1 contributed, SFBR scientists gain another \$8 in competitive grant support, making our researchers among the most productive anywhere.
- ▷ **Critical programs and projects.** Research grant and contract funding is the majority funding source of SFBR, totaling about 75 percent of our revenue. The remaining support must come from endowment income and current donations.
- ▷ **Key research ventures.** Donations fund recruitment of key scientists and pilot studies, each representing strategies that encourage bold initiatives by new and existing faculty.
- ▷ **Extraordinary resources.** SFBR has a history of developing rare scientific resources. The AT&T Genomics Computing Center and the BSL-4 maximum containment laboratory are examples of such resources funded by donations.
- ▷ **Technology.** Modern research is made more productive by the latest in technology. The higher cost of the newest technology usually requires philanthropic support.
- ▷ **Make the difference.** Unlike some research organizations, SFBR must rely on donations as the sole source for funding new programs and capital. SFBR does not have patient or tuition revenue or direct governmental allocations to fund capital and operating expenses.

SFBR excels as a center for scientific research because of the philanthropic support of our donors. Will you consider becoming our partner in progress? In addition to donor opportunities highlighted in this report, such as the Golden Circle, The Argyle, Founder's Council and Southwest Foundation Forum, the Foundation offers opportunities for legacy gifts, capital and endowment gifts, and memorial and honor gifts.

For more information on any of these giving opportunities, contact SFBR's chief development officer, Mr. Corbett Christie, at 210-258-9870 or cchristie@sfbr.org, or visit our Web site at www.sfbr.org and click on "Support SFBR."



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