SFBR

report of progress in 2005

southwest foundation for biomedical research

About SFBR

As one of the world's leading independent biomedical research institutions, the Southwest Foundation for Biomedical Research is dedicated to advancing human health through innovative biomedical research. Today, SFBR's multidisciplinary team of nearly 75 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 infectious diseases.

SFBR is the site of the Southwest National Primate Research Center and home to the world's largest baboon research colony. The Foundation enjoys a distinguished history in the innovative, humane and appropriate use of nonhuman primates 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 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. Seventy percent of its annual budget is funded from competitive, peer-reviewed grants, while another 12 percent comes from contracts with biotechnology and pharmaceutical firms. Remaining expenses must be met by the generous contributions of foundations, corporations and individuals, as well as earnings from SFBR's permanent endowment.

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.

Table of contents

SFBR

Southwest Foundation for Biomedical Research

Credits

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Letter from

the President

For nearly 65 years, scientists at Southwest Foundation for Biomedical Research have devoted themselves to the race for discoveries that will improve human health and save lives. In this important effort, 2005 was a year of great accomplishment.

The Foundation's research teams poured their energy, creativity and expertise into nearly 200 major research projects tackling the gamut of maladies that plague our world: common complex diseases such as cardiovascular disease and diabetes; infectious diseases such as AIDS, hepatitis, and SARS; bio-threat agents such as anthrax and Ebola; as well as psychiatric disorders, diseases of the premature newborn, and other ailments.

A standard measure of our scientists' success is the amount of grant and contract income they generate, since awards from the National Institutes of Health and other funding organizations are always highly competitive. In this area, SFBR scientists rank among the top echelon of their peers. Total grant income to SFBR reached $39.5 million in 2005, up from $37.5 million in 2004. Likewise, new grant and contract awards to SFBR scientists continued at a high level, reaching $32.3 million.

Of course, the truest measure of success is scientific accomplishment. Here again, our scientists excelled, contributing more than 130 publications to the scientific literature. Consider just a few of the major findings you will see highlighted in this annual report.

An international team of researchers led by Dr. John Blangero and other SFBR geneticists published a discovery in *Nature Genetics* explaining how the SEPS1 gene regulates inflammation. Because inflammation plays a role in virtually every major disease, this finding opens up many potential avenues for intervention on a broad range of health issues, including cancer, heart disease, diabetes, Alzheimer's and infections.

Dr. Krishna Murthy co-authored a publication in *Science* outlining evidence that individuals with multiple copies of an immune-response gene known as CCL3L1 appear to have added protection against infection with HIV. Those who do become infected show slower progression to AIDS. In a separate effort, Dr. Murthy has joined with collaborators in New York and California on an NIH-funded project to test a candidate AIDS vaccine that looks promising as a global vaccine, meaning it could be effective against all the various sub-types of HIV. It also shows potential as both a preventive and a therapeutic vaccine.

The antiprogestin CDB-4124, previously conceived and synthesized by Dr. P.N. Rao, was the subject of a patent awarded to SFBR in 2005. Under the tradename Proellex™, this compound has been licensed to Zonagen Inc. for development in the treatment of uterine fibroids, endometriosis and progesterone-dependent tumors. Zonagen has completed European clinical trials with the compound, and results published in 2005 indicate that it significantly reduces the size of fibroids without harmful side effects.

Meanwhile, Dr. Henry McGill teamed up with local and national collaborators to publish a scoring system that can be used by family physicians to assess a person's risk of advanced atherosclerotic lesions (hardening of the arteries) before he or she shows symptoms of cardiovascular disease.

Clearly, SFBR scientists are blazing new trails in the quest for life-saving and life-improving discoveries, and the Foundation is working to give them every advantage in their efforts. Adding to a collection of extraordinary resources that include the Southwest National

Primate Research Center, the nation's only privately owned BSL-4 laboratory, and the AT&T Genomics Computing Center, SFBR is completing the total renovation and modernization of its campus, a venture started under the tenure of Dr. Frank Ledford.

In 2005, SFBR dedicated the Ledford Building, a new state-of-the-art laboratory and office complex, and commenced the final phase of planned renovations to the Slick-Urschel Laboratory Complex, which will house Genetics Department laboratories and offices and the Northrup Memorial Library. We expect to dedicate these facilities in the fall of 2006.

It speaks volumes about SFBR's friends and supporters that we have been able to complete more than $50 million in campus improvements and renovations without incurring any debt. In addition, with the strong support of our donors, the Foundation's endowment now exceeds $80 million, placing it in a very strong position to compete for and support the most gifted scientists.

Philanthropy is key to the financial strength of SFBR, allowing us to advance our scientific programs in a way that cannot be done with research grants alone. On behalf of the Board of Trustees and the faculty and staff at SFBR, I offer my sincere thanks to all of you, our partners in progress.

We recently announced a number of changes in leadership at SFBR. As a result, I have agreed to serve as president on an interim basis until we embark on a search for new leadership. I value the support and cooperation of the faculty and staff as well as the Board of Trustees as together we strive to build upon SFBR's strong foundation and lead the organization to even greater future achievement.

Respectfully submitted,

John C. Kerr

John C. Kerr
President and Chairman

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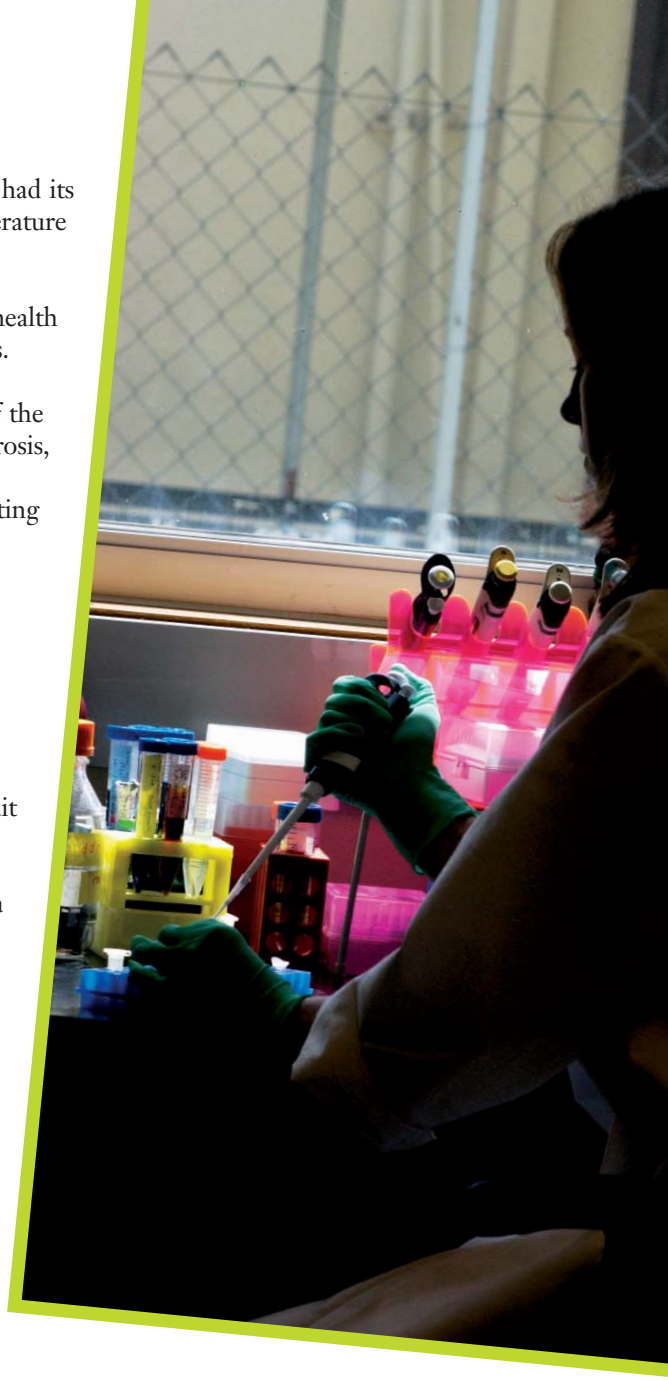
department of

genetics

The Department of Genetics had its best year ever in 2005, producing 84 contributions to the scientific literature and generating over $16 million in grant and contract income. This outstanding level of achievement by the scientists and staff resulted in considerable progress in the department's mission to improve human health through basic biomedical research with animal and human populations. Innovative research efforts led to major advancements in methods development, animal model development, and in our understanding of the genetic determinants of a broad range of diseases including atherosclerosis, obesity, diabetes, and osteoporosis. In addition to the active research programs in the department's traditional areas of strength, several exciting new avenues of research were opened up this year.



Assessing genetic determinants of complex diseases

Assessments of the genetic determinants of common complex diseases generally involve three stages of analysis. First, quantitative genetic studies determine that genes do, in fact, exert an influence on the disease of interest. Second, the individual genes influencing the trait are localized to specific chromosomal regions using linkage analysis. Finally, the individual genes and the variants within those genes that influence a disease-related trait are identified and characterized using a state-of-the-art combination of statistical and molecular genetic techniques.

Departmental scientists contributed to 13 gene localizations published in the scientific literature in 2005. These genes are involved in a broad range of common disease processes, including cholesterol metabolism, oxidative stress, hemostasis and fibrinolysis, diabetes and insulin resistance, obesity, glaucoma, and osteoporosis. In addition to these intriguing results, departmental scientists made dramatic strides in moving from gene localization to gene identification, contributing to a total of eight gene identifications published during 2005. These genes are involved in alcoholism, diabetes, osteoarthritis, lupus, hemostasis, mitochondrial dysfunction and inflammation.

Major findings and new projects related to cardiovascular disease

Historically, the primary focus of research in the Department of Genetics has been on cardiovascular disease and associated risk factors, and this remained true during 2005. Departmental scientists generated a total of $6.7 million to support research projects on heart disease and related factors, and there were several major scientific accomplishments in this area.

Discovery of inflammation gene and its mechanism of action. The powerful combination of the department's strengths in statistical genetics and molecular genetics facilitated the identification and characterization of a gene influencing inflammation processes, which are critical in heart disease.

In a study directed by Dr. John Blangero, Dr. Joanne Curran and colleagues discovered a direct mechanistic link between a novel gene, selenoprotein S, and the production of inflammatory cytokines that are critically involved in several common diseases, including atherosclerosis and diabetes. These findings were published in the prestigious journal *Nature Genetics* and were made possible by a highly innovative statistical genetic technique that

Dr. Blangero developed for the purpose of identifying functional variants from DNA sequence information.

Determining the interplay among genes, hormones and obesity. In a novel project directed by Dr. Tony Comuzzie, Dr. Liz Tejero completed a search for genes influencing gene expression for a hormone found in fat tissue in baboons. In recent years, it has been discovered that, rather than being inert, fat is a metabolically active tissue, the characteristics of which have a strong influence on the risk for diabetes and other metabolic diseases. Resistin is a hormone that is secreted by fat tissue and that has been implicated in risk for obesity and diabetes in several animal and human studies. Levels of gene expression for resistin correlate strongly with obesity.

Dr. Tejero and colleagues were interested in whether or not there is a genetic component to gene expression for resistin in baboons. The unique pedigreed baboon colony at SFBR is ideally suited for addressing this question, since the study required the sampling of fat tissue from a large number of family members for which extensive genetic data were available. The research resulted in the localization of a gene influencing resistin gene-expression levels.

Scientists find genetic contributor to thrombosis. Drs. Laura Almasy and John Blangero, who direct a study of the genetic determinants of thrombosis in a Spanish population, published a study that localized a gene influencing clotting factor VII levels and then identified the specific variants in the gene's DNA sequence that are responsible for the variation. The resulting paper is one of a handful of studies in the literature that have fully identified and characterized a gene responsible for variation in a quantitative, or measurable, trait.

Project on coronary artery disease takes researchers to Alaska. A major new grant award was received in 2005 to support continued research on a project titled "Genetics of Coronary Artery Disease in Alaska Natives." This grant was awarded to Dr. Jean MacCluer by the National Heart, Lung and Blood Institute of the National Institutes of Health. This award will allow research on the genetic determinants of heart disease in Alaska Natives living in villages in the Norton Sound area of Alaska to continue through 2010. The grant also strengthens the department's focus on cardiovascular disease in minority populations.

Animal models advance studies on human health

The department has a long history in animal model development, which was the second most highly funded area of research during 2005, with grant income of $2.4 million received during the calendar year.

Mapping the rhesus genome. In order to localize genetic effects to specific chromosomal regions, scientists require that a map of locations of genetic markers be available. Departmental scientists developed such a map for baboons several years ago, and this map has facilitated rapid advances in the detection of genes influencing a broad range of common disease processes in the baboon model. Dr. Jeff Rogers pioneered the baboon gene mapping effort, and this year he received a major grant from the National Center for Research

Resources to develop a linkage map for another primate commonly used in research, the rhesus macaque. This work promises to have a tremendous impact on the range of genetic research that can be conducted with macaques.

Testing a potential tuberculosis vaccine in rhesus macaques. Rhesus macaques are the focus of a new grant received in 2005 from the National Institute of Allergy and Infectious Diseases titled "TB Vaccine Development in a Nonhuman Primate Model." Dr. John VandeBerg directs this study, which is using the macaque as an animal model for the development of a tuberculosis vaccine. Tuberculosis is the one of the world's leading infectious disease killers, resulting in 2 million deaths a year. Each year, 54 million people are infected with TB, and 8 million individuals develop clinical disease. An effective vaccine is needed urgently to address this international public health problem.

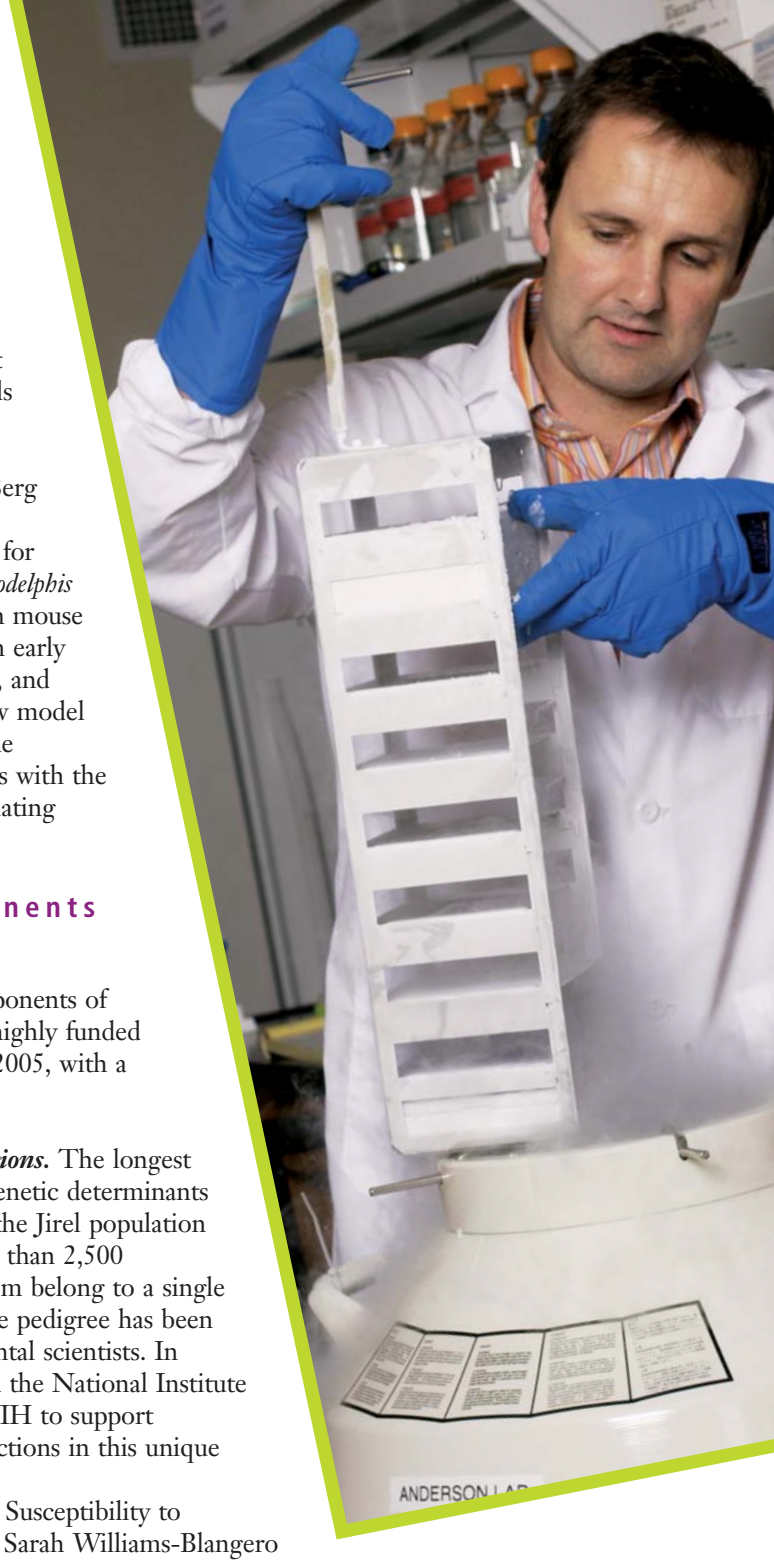
Dr. VandeBerg's study is a collaboration involving prominent TB researchers from Brazil and the specialized nonhuman primate facilities of the Southwest National Primate Research Center. If successful, this new vaccine could have a huge impact on improving health in our global community.

Baboons make natural model for epilepsy studies. Dr. Jeff Williams directs a study focused on developing the baboon as an animal model for research on epilepsy. Along with colleagues from the University of Texas Health Science Center at San Antonio and from the Southwest National Primate Research Center, Dr. Williams published the first comprehensive electro-clinical assessment of spontaneous seizures and epilepsy in baboons. This work documented that spontaneous seizures in baboons are highly similar to those observed in humans, and thus established that the baboon is an outstanding model for research on this important disease. This critical first step will allow Dr. Williams to pursue his goal of identifying the genes that contribute to human epilepsy using the baboon model.

Advances in cancer research with the laboratory opossum. Nonhuman primates are not the only animal models used by departmental scientists. The South American opossum *Monodelphis domestica* was developed as a laboratory animal by Dr. John VandeBerg. The

laboratory opossum has been a widely used model for research on development, cancer and cardiovascular disease. In 2005, Dr. VandeBerg received a generous grant from the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation for the continued maintenance and research use of Southwest Foundation's colony, which provides animals to laboratories throughout the world for collaborative research programs.

Drs. Brad Wang and John VandeBerg published a key report in 2005 on the development of the *Monodelphis* as a model for cancer research. They discovered that *Monodelphis* can become immunologically tolerant when mouse melanoma cells are injected into them at an early age. The melanomas can grow, metastasize, and persist in the laboratory opossum. This new model for cancer research will enable studies of the interactions of tumor growth and metastasis with the host's immune mechanisms aimed at eliminating cancers.



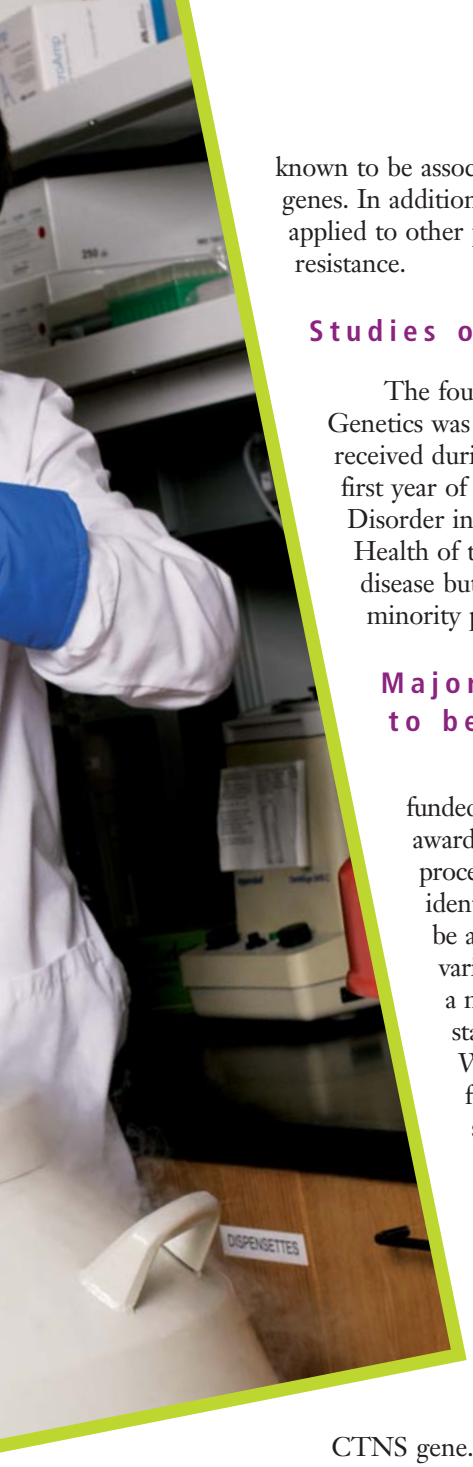
Uncovering genetic components of infectious disease

Investigations on the genetic components of infectious disease made up the third most highly funded area of research in the department during 2005, with a total of $2.1 million awarded.

Fighting off parasitic worm infections. The longest running project in this area concerns the genetic determinants of susceptibility to helminthic infection in the Jirel population of eastern Nepal. This study involves more than 2,500 members of the Jirel population, all of whom belong to a single pedigree, or documented family group. The pedigree has been fully genetically characterized by departmental scientists. In 2005, a new grant award was received from the National Institute of Allergy and Infectious Diseases of the NIH to support continued research on intestinal worm infections in this unique pedigree.

The project, "A Genome Scan for Susceptibility to Helminthic Infection," was awarded to Dr. Sarah Williams-Blangero and will yield new insights into the genetic determinants of susceptibility to these infections, which affect a quarter of the world's population and can cause serious deficits in growth and cognitive development in children.

Waging an uphill battle against drug-resistant malaria. Dr. Tim Anderson has focused his research in the area of infectious disease genetics on the genetic components of drug resistance in malaria parasites. Malaria kills a million people each year, and drug resistance is a critical barrier to eliminating this global health threat. In an innovative article published in 2005, Dr. Anderson suggested a population genetic approach for identifying genes that are involved in antimalarial drug resistance. He tested the method utilizing information on loci



known to be associated with drug resistance in malaria parasites as compared to neutral genes. In addition to being useful for malaria research, this general approach can be applied to other pathogens that are public health problems because of emerging drug resistance.

Studies on psychiatric disease

The fourth most highly funded area of research in the Department of Genetics was in the genetics of psychiatric disease. A total of $1.3 million was received during 2005 to support research on this topic. These funds included the first year of a new grant awarded to Dr. Laura Almasy, "Genetics of Bipolar Disorder in a Latino Population," awarded by the National Institute of Mental Health of the NIH. This work not only expands ongoing research in psychiatric disease but also adds to the department's significant focus on health issues in minority populations.

Major advance in statistical methods to benefit genetic research

Genetic epidemiological methods development is the fifth most highly funded area in the Department of Genetics, with a total of $1.27 million awarded in 2005 to support research on this topic. As noted above, the process of moving from localization of a gene influencing a disease to actual identification of the gene is still in its infancy. This process requires that one be able to find the changes in DNA within a gene, or the functional variants, that have a direct impact on the disease trait being considered. In a major theoretical advance, the department's world-renowned team of statistical geneticists, including John Blangero, Harald Göring, Jeff Williams, Laura Almasy, and Tom Dyer, developed a statistical method for predicting the most likely functional variants in a gene given sequence data. This method has already been integrated into the SOLAR software package produced and distributed by the statistical genetics team and is facilitating new genetic discoveries in laboratories across the globe.

New and growing areas of research

Cystinosis. One of the most exciting new areas of research opened up during 2005 is focused on the study of cystinosis. This disease is a monogenic disorder involving disruption of the CTNS gene. The major complication of cystinosis is severe kidney disease at an early age, which often results in the need for kidney transplantation. Departmental scientists are using a highly innovative approach to look for novel mechanisms involved in this devastating disease.

Drs. Eric Moses and John Blangero are adapting the methods of complex disease genetics to discover genes that are located near the CTNS gene. These genes are then being evaluated for their role in modifying disease severity or determining the various symptoms of the disease. In this effort, Dr. Moses has employed cutting-edge technology that allows him to measure levels of gene expression in tens of thousands of genes at a time in order to identify all of the genes involved in the biological pathways underlying the disease processes associated with cystinosis. Funding for this pioneering project has been provided by the Azar and Shepperd families, whose generous contributions are facilitating rapid progress in our understanding of the complex genetic factors influencing cystinosis.

Diabetes and metabolic syndrome in children. Research on diabetes has been an area of growing importance in the department for several years and was responsible for $469,200 in grant income during 2005. This effort is spearheaded by Dr. Ravi Duggirala, who has conducted extensive research on the genetics of the metabolic syndrome and risk factors for type II diabetes in Mexican Americans. While type II diabetes has traditionally been thought of as a disease that develops in adulthood, changing dietary and exercise patterns have resulted in the disease being observed increasingly in children. However, little research has been conducted on metabolic syndrome and type II diabetes in children. This year, Dr. Duggirala received a major grant from the National Institute for Child Health and Development of the NIH for a groundbreaking study titled "Metabolic Syndrome in Mexican American Children." This project will be the first large-scale genetic epidemiological study of metabolic syndrome and type II diabetes in Mexican American children.

Osteoporosis. Osteoporosis and bone biology is a growing area of research within the department, responsible for a total of $305,943 in income during 2005. This area shows great potential for growth and new funding. One of the most important measures used by clinical practitioners to assess risk for osteoporosis-related bone fractures is bone mineral density. In an effort led by Drs. Michael Mahaney and Lorena Havill, departmental investigators located a gene influencing normal variation in forearm bone mineral density utilizing the pedigreed baboon model. The chromosomal region where the gene is located corresponds to the same region influencing bone mineral density in humans. This finding is the first result of a genome scan for bone mineral density in nonhuman primates, and it verifies the value of the baboon as an animal model for genetic studies on osteoporosis.

Going forward

The major achievements of departmental scientists during 2005 indicate that the Department of Genetics will continue to be a leading center for genetic research on complex diseases in 2006 and beyond. The powerful resources that the Department of Genetics has

created, including its computing resources, analytical techniques, genetically well-characterized human study populations and novel animal models, provide unparalleled opportunities for research aimed at identifying the genes responsible for the major public health problems that impact the developed and developing worlds. In addition to this exceptional research environment, the department has an outstanding team of scientists and scientific support staff who together have taken maximal advantage of this environment to advance science in the area of genetics. In 2005, all these factors came together to facilitate the significant discoveries in both established and new research programs.

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(as of December)

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John L. VandeBerg, Ph.D.

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department of

virology

From established global killers such as AIDS and hepatitis to emerging threats such as SARS and Ebola, scientists in the Department of Virology and Immunology are devising and testing strategies to defeat deadly pathogens. These dedicated researchers want to make the fear and misery of infectious diseases a thing of the past, and they have some of the world's best resources at their disposal as they pursue their worthwhile investigations.

These resources include the nation's only privately owned biosafety level four (BSL-4) laboratory. The safest type of laboratory in the world, the BSL-4 is designed for maximum containment and allows scientists to study deadly pathogens for which there are no current vaccines or treatments. Also extremely valuable to the department's efforts are the nonhuman primates at SFBR's Southwest National Primate Research Center. These animals offer the most effective models for human infectious disease, as well as for the evaluation of therapeutic drugs and vaccines against viral agents.

AIDS

Vaccine studies. For nearly two decades, conventional approaches to develop an effective vaccine against HIV and AIDS have failed. That is why the National Institute of Allergy and Infectious Diseases of the NIH has encouraged research teams to "think outside the box" in the development of new vaccine approaches. Dr. Krishna Murthy is part of a newly funded HIV Vaccine Design and Development Team, together with United Biomedical Inc. and the California Department of Health. The group has developed and is testing a novel candidate vaccine that induces the production of antibodies that bind with the CD4 receptor complex, which is used by a protein in HIV's coating structure to bind with immune cells called T 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. With this ability, the vaccine has the potential to be effective against all subtypes of HIV and to be used for both preventive and therapeutic purposes. Preliminary studies in guinea pigs have produced very encouraging results, and now immunogenicity studies in baboons are being planned.

In a separate effort, Dr. Luis Giavedoni, in collaboration with Dr. Erwin Goldberg from Northwestern University, Dr. Mark Saltzman from Yale University, and Dr. Hong Shen from Washington University, performed a study in rhesus macaques to evaluate immunogenicity conferred by a controlled-release DNA vaccine applied to different mucosal surfaces (nasal and vaginal). Although antibody and humoral responses against the simian form of HIV (SIV) were not detectable after the series of DNA immunizations alone, they seemed to "prime" the animals' immune response and improve the effectiveness of a subsequent booster immunization with a recombinant viral vaccine. Tests also indicated that the nasal route of primary immunization is more efficient than the vaginal one.

Deciphering the intricacies of the proper immune response. Understanding how HIV causes AIDS in humans has mystified AIDS researchers for more than 20 years. Dr. Jon Allan's laboratory has approached this problem by studying a related simian immunodeficiency virus (SIV) in a unique group of monkeys living in sub-Saharan Africa. These African green monkeys are naturally resistant to disease, unlike Asian macaques, which develop classical AIDS.

Surprisingly, African monkeys do not control infection via a strong, potent immune response. Rather, the virus replicates to very high levels in the blood of chronically infected animals. Dr. Allan's group has determined that one remarkable difference between susceptible and resistant hosts lies with differences in the absolute number of immune cells available for infection by SIV. African monkeys naturally limit the number of the key target cells in their system, by several mechanisms, thus limiting virus killing of those cells.

If left unchecked in Asian macaques, massive killing of these T cells and chronic immune activation leads to AIDS. In collaboration with Dr. Giavedoni's laboratory, Dr. Allan is investigating the cellular immune response's role in fighting AIDS in monkeys. Another key factor in host resistance to AIDS may lie with fundamental differences in the host immune response to infection. Cellular immune responses initially limit viral replication and AIDS in a susceptible host; however, viral escape from detection ultimately results in round after round of cell killing, T cell depletion, and opportunistic infections. In fact, there are profound differences not only in the magnitude of this response, but also in specificity. Each monkey species recognizes distinctly different viral genes. Theoretically, predominant immune responses could determine outcome from infection. These studies are presently focused on teasing out the delicate balance between infection, cell killing, and preservation of health.

Hepatitis C

The hepatitis C virus (HCV) was discovered nearly 15 years ago and continues to infect approximately 200 million people worldwide, serving as the leading cause of liver disease in the United States. As of yet, there is no effective vaccine for the prevention of infection. Two potential candidate vaccine strategies are being investigated at SFBR under the leadership of Dr. Krishna Murthy in collaboration with investigators at the National Institutes of Health.

The first vaccine utilizes a non-infectious, virus-like particle that structurally resembles HCV. Four chimpanzees were immunized with the vaccine and exhibited an enhanced immune response that included T cell response and IFNγ production in the liver as well as an HCV-specific antibody response. Upon challenge with the virus, two of the animals resisted infection, while the other two developed transient infection that was controlled over time. Now the research team is planning studies to determine if the vaccine offers broad protection against divergent strains of HCV.

The second HCV vaccine strategy consists of administering a primary dose of a DNA vaccine containing selected genes of HCV, followed by a booster shot containing a mixture of HCV proteins. Two chimpanzees were immunized utilizing this approach and were later challenged with a high dose of infectious HCV. Results were mixed. However, both these studies established that robust T cell and IFNγ responses correlated with protection and that it is possible to develop a preventive vaccine for HCV.

Hepatitis B

Hepatitis B virus (HBV) infections represent a major worldwide health problem due to the predilection of this virus to cause lifelong chronic infections. Ten percent of infected adults and 95 percent of infected newborns become chronic carriers. The chronic infections frequently progress to cirrhosis and liver cancer. Worldwide there are an estimated 350 million chronic carriers of HBV, making HBV infections the fourth-leading cause of death due to infectious diseases, being surpassed only by tuberculosis, malaria and diarrhea in young children. The only animal model for HBV infection is the chimpanzee.

Despite several decades of research by numerous laboratories, the cellular receptor that

HBV uses to gain entry into cells has not been identified. Dr. Robert Lanford and his research team have developed tissue-culture systems based on primary hepatocytes from humans and chimpanzees to aid in their efforts to identify the cellular factors involved in receptor interactions. This year, the team identified a short region of the large envelope protein of HBV that is involved in receptor interaction. They were able to synthesize a short peptide mimicking this region of the HBV envelope that can block infection by HBV, presumably by interacting with the cellular receptor. The current goal is to use the peptides to capture and identify the receptor. Identification of the HBV receptor would provide new approaches to block replication of the virus and develop new antivirals for the treatment of chronic infections.

Biodefense

Providing resources and expertise. Even before the threat of terrorist attacks on U.S. soil became all too real in 2001, Dr. Jean Patterson and her laboratory at SFBR were working on projects to help defend the nation from the threat of bioterror. Since that time, Dr. Patterson and her team have taken on an expanded role in this area, especially after SFBR was designated in 2003 as part of the Western Regional Center of Excellence for Biodefense and Emerging Infectious Diseases. With the Biosafety Level 4 Core and the Small Animal Core for this 16-member consortium that spans five states, SFBR provides important resources and expertise to other consortium members.

Currently, Dr. Patterson's laboratory is developing an *in vitro* assay for screening inhibitory RNA molecules that can be used as a treatment for Ebola hemorrhagic fever, and together with researchers at Emory University, the group is developing neutralizing antibodies to Lassa hemorrhagic fever. Additionally, they have developed or contributed to the development of a number of animal models for biodefense research, including a guinea pig model for Nigerian strains of Lassa hemorrhagic fever viruses, a new small nonhuman primate model that emulates human Lassa fever, and the marmoset model for the eastern equine encephalitis virus.

Advances in vaccine and therapy development. In a separate collaboration with researchers at the Institute of Human Virology at the University of Maryland in Baltimore, Dr. Jean Patterson's team has provided data showing the efficacy of a reassortant Lassa fever vaccine. A single dose of the vaccine conferred 100 percent protection to guinea pigs, which showed complete immunity to the disease, even when challenged with divergent strains of the Lassa virus, and even when the vaccine and the challenge were administered simultaneously.

The group has continued to refine an anthrax antitoxin that was developed in collaboration with researchers at the University of Texas at Austin, with great success. Tests with guinea pigs given a lethal dose of inhalation anthrax showed that a subcutaneous injection of this high-affinity recombinant antibody successfully eliminated both anthrax bacteria and its deadly toxins from the body, leaving the treated animals healthy with no signs of infection two and three weeks later. If further tests produce similar results, this antibody could be used to provide the first successful treatment for late-stage anthrax, even for a strain that has been designed to resist antibiotics.

Assisting national research efforts. In support of the nation's biodefense programs, Dr. Patterson and her team work with the Department of Defense to determine surface survival kinetics of bioterror agents such as the hemorrhagic fever viruses Ebola, Marburg and Lassa. In addition, they have been involved in characterizing spore coat proteins of anthrax in an attempt to generate proteomic profiles that can be used to delineate various anthrax strains or variants.

Finally, their work with private companies has included the generation of antigens from bioterror agents that will be used in detection assays as well as the testing of a proprietary air filtration system that could ultimately be used to not only purify contaminated air but also kill trapped viral particles.

Emerging and exotic viruses

West Nile virus. West Nile virus, which reached New York in 1999 and has since spread to all of the contiguous 48 states, is one of the major causes of encephalitis in elderly persons. There is no effective vaccine, and although the mouse is used as a research model, it does not truly reflect the outcome of infection in humans. A random serological survey of baboons at SFBR showed a seroprevalence of 38 percent, suggesting that baboons are susceptible to West Nile virus infection by natural exposure. Now Dr. Krishna Murthy is working in collaboration with Dr. Maria Rios of the FDA to examine how the virus replicates in baboons and to determine whether the baboon would serve as a good animal model for studying West Nile virus and potential therapies.

Dengue. The need for models of dengue disease has reached a pinnacle, as the transmission of this mosquito-borne virus has increased dramatically. Little is known about the mechanisms that lead to dengue fever and its more severe form, dengue hemorrhagic fever; this is due to the fact that only humans show signs of disease. In the last five years, research by Dr. Rebeca Rico-Hesse's laboratory has better identified the initial targets cells of infection, and this has led to the development of models of infection in primary human cell cultures (from blood

donors). Mouse-human chimeras, containing these target cells, have helped the group develop the first animal model of dengue fever. These advances should soon end the stalemate in testing antivirals and vaccine preparations that had necessarily been done in incomplete or irrelevant models. This research was funded by the Ellison Foundation and the National Institutes of Health.

Dengue viruses causing severe, hemorrhagic disease have displaced less virulent strains in the Americas, and NIH-funded research by Dr. Rico-Hesse may partially explain why. Her research team has shown that the more virulent Southeast Asian variant of dengue replicates and appears in the salivary glands of the vector mosquito *Aedes aegypti* more quickly than the less-virulent American strain. This means that mosquitoes that bite a person infected with the more virulent strain are able to transmit the deadlier virus to other people more rapidly than they can the less virulent strain. From an ecological or epidemiological perspective, this may be one reason why more virulent strains of dengue virus displace less virulent viruses. Thus, the occurrence of dengue hemorrhagic fever will likely continue to increase in this continent and others.

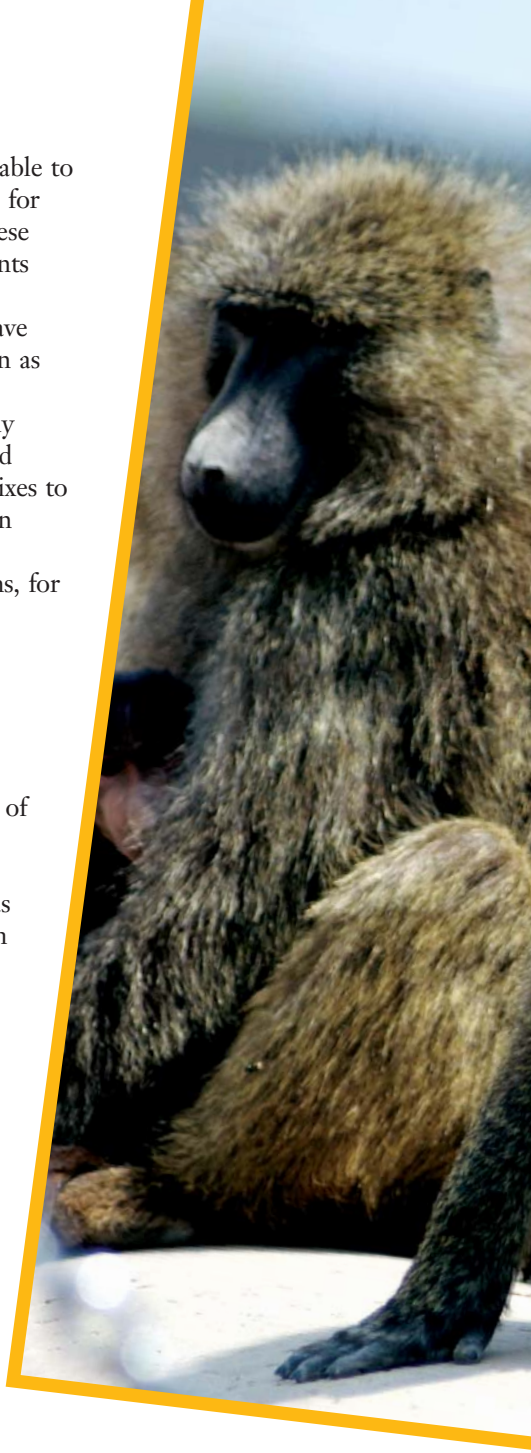
Engineering antibodies as a new way to detect and defeat SARS and other emerging bio-threats. As previously unknown viruses such as SARS emerge and spread around the globe, and while other deadly viruses, such as Ebola, pose new threats through periodic outbreaks or the possibility of their use by terrorists, new methods are needed to help communities, first responders, hospitals, public health officials, and the military to detect, diagnose, and ultimately treat them. With this in mind, Dr. Andrew Hayhurst is developing recombinant antibodies as diagnostics and therapeutics to emerging viruses, particularly those for which there is no current vaccine or treatment.

In one area of this research, Dr. Hayhurst has genetically fused a novel reporter enzyme to SARS-specific single-chain antibodies to offer a new route to super-sensitive SARS diagnostics. This new technology will offer pathways to novel imaging applications both *in vitro* and *in vivo*. In the laboratory, Dr. Hayhurst has shown that these novel genetic constructs detect minute quantities of SARS particles within five minutes when used with the ELISA plate-based detection method. Unsatisfied, he is striving for quicker detection by using a new but exceptionally simple modification of the basic ELISA immunoassay. In this manner, he aims to develop a high-quality method of detection equivalent to nucleic acid-based amplification systems at a fraction of the cost and time. Besides its application to SARS, this and other methods being developed by Dr. Hayhurst can be applied to a wide range of antigens, including other viruses and cancer cell markers, simply by switching the specificity of the antibody.

In collaborative research with the Naval Research Laboratories, Dr. Hayhurst is using a recently discovered type of antibody cloned from llamas (called a single-domain antibody) in hopes of being able to equip frontline defenders with a new generation of biosensors that are portable, reusable and able to withstand extreme field conditions, such as high heat. He has created a large library of single-domain antibodies in the laboratory at SFBR and has been testing them for proof-of-concept. Thus far, he has demonstrated that they are able to withstand boiling, indicating their durability. He also has been screening them for their ability to detect live viruses, while the Naval Research Laboratories have been testing them on toxins.

It is anticipated that these rugged antibodies will be highly applicable to improving the shelf lives of diagnostic assays and negate the need for refrigeration. Furthermore, the remarkable thermo-stability of these antibodies should make routine biosensing in extreme environments possible.

In yet another effort, Dr. Hayhurst and his laboratory have assembled a synthetic human-single-chain-antibody library, known as ALAMO #1, that is rapidly delivering binders specific for chosen antigens. In SFBR's biosafety level 4 laboratory, he has successfully isolated polyclonal antibody mixes specific for live SARS-CoV and Marburg virus, and he is currently untangling these polyclonal mixes to obtain monoclonal antibodies for incorporation into neutralization assay trials *in vitro*. It is anticipated that cocktails of neutralizing antibodies will confer passive immunity to counter these infections, for which no vaccines or therapeutics currently exist.



Children's health

Lung disease in premature infants. The laboratory of Dr. Luis Giavedoni has collaborated intensively with the multi-institutional group that uses the premature baboon animal model of bronchopulmonary dysplasia (BPD), a lung disease that threatens the lives of many premature human infants. Using a combination of reagents developed in Dr. Giavedoni's laboratory, the group has demonstrated in premature baboons that delay of extubation from low tidal volume positive pressure ventilation (LV-PPV) to nasal continuous positive airway pressure (nCPAP) results in accumulation of proinflammatory cytokines in bronchoalveolar lavages. These data are important, because they provide additional support to efforts to avoid ventilating premature infants if at all possible following delivery, or, when ventilation is necessary, to wean the infants as soon as possible to nCPAP.

Developmental programming. Dr. Luis Giavedoni collaborates with Drs. Peter Nathanielsz and Natalia Schlabritz, director and member, respectively, of the Center for Pregnancy and Newborn Research at the University of Texas Health Science Center at San Antonio, on their investigations in the area of developmental programming, or how the development of the fetus in the womb can impact that individual's health for a lifetime. In one such investigation, Dr. Giavedoni's work demonstrated that pregnant female baboons that were exposed to glucocorticoid injections similar to the ones applied to pregnant women with risk of premature delivery present quantitative differences in lymphocyte phenotype at the time of delivery. The betamethasone treatment of pregnant females with no indication of preterm labor altered some components of the fetal and maternal immune system. The long-term consequences of these alterations are not known, but the use of the baboon model will permit such studies to be completed.

New initiatives

Schistosomiasis. In October 2005, SFBR officially opened the Ledford Building, a new office and laboratory building to support schistosomiasis research led by Dr. Philip T. LoVerde. The building's opening allowed Dr. LoVerde to move his research team from the State

2005 Doctoral Staff

(as of December)

Chair
Jean L. Patterson, Ph.D.

Scientists
Jonathan S. Allan, D.V.M.
Robert E. Lanford, Ph.D.
Philip T. LoVerde, Ph.D.
Krishna K. Murthy, D.V.M., Ph.D.
Rebeca Rico-Hesse, Ph.D.

Associate Scientist
Luis D. Giavedoni, Ph.D.

Assistant Scientist
Andrew Hayhurst, Ph.D.

Staff Scientists
Ricardo Carrion Jr., Ph.D.
Vida L. Hodara, Ph.D.

Postdoctoral Scientists
Justin R. Anderson, Ph.D.
Dennis Bente, D.V.M.
Claudia C. Queiroz, Ph.D.
Azeneth B. Sexauer, Ph.D.
Wenjie Wu, Ph.D.

University of New York at Buffalo to SFBR, where he and his team continue their search for a vaccine against a disease that ranks with malaria and tuberculosis in global health importance.

This parasitic disease, spread by freshwater snails, is endemic in Africa, the Middle East, South America (primarily Brazil), the West Indies and Asia (primarily China and the Philippines). It is a major cause of morbidity, or illness, around the world, and claims the lives of 800,000 people each year.

Dr. LoVerde's research has progressed to the point that he is studying promising candidates for a vaccine, which would greatly benefit people worldwide who are continually exposed to the opportunity for re-infection following antibiotic treatment. His initial work at SFBR focuses on three vaccine candidates that have proved effective in mice and hamsters. Now he is examining their safety and efficacy in nonhuman primates, particularly the baboon.

department of

physiology and medicine

Research in the Department of Physiology and Medicine focuses on two major areas of biomedical research, cardiovascular diseases and cancer drug discovery. Several new advances in each of these areas were realized during 2005. As in the past, a common feature of these research efforts is extensive collaboration with investigators from other departments at SFBR as well other institutions throughout the United States and the world.

Cancer drug discovery

The drug discovery program under the direction of Dr. Susan Mooberry at the Foundation focuses on finding new drugs that may be useful in the treatment of cancer. In the past year, she and her laboratory identified several different classes of natural and synthetic compounds and evaluated them for activities that may predict anticancer effects. The initial step used in this research is to examine the effects of previously unscreened compounds on cellular structures called microtubules. Microtubules are used by cells to guide genetic material during the cell divison process. Disruption of microtubule function inhibits cell division and signals cancer cells to initiate apoptosis, or cellular death. The type of disruption of microtubule function that has been shown to be the most promising in terms of cancer treatment is a stabilization of microtubule formation that subsequently prevents cell division and leads to cellular death.

In 2005, Dr. Mooberry continued her collaboration with Dr. Paul Wender at Stanford University and screened several additional new analogs of laulimalide, a microtubule stabilizer identified by Dr. Mooberry in extracts from a marine sponge. Current studies are designed to determine which of these have the optimum characteristics for consideration of clinical development.

In another collaboration with Dr. Milton Brown at the University of Virginia, analogs of another promising new drug, combrestatin, were screened in Dr. Mooberry's laboratory. Combrestatin is a unique type of microtubule-interacting drug because it also has anti-vascular effects. This could represent a new mechanism for tumor destruction. Dr. Brown's laboratory has added modifications to the original compound to improve solubility, and subsequent functional studies in Dr. Mooberry's laboratory have shown that this modification has not diminished its anti-tumor activity.

Also in 2005, Dr. Mooberry's program expanded its ability to find potential new cancer-fighting drugs by accessing libraries of synthetic as well as marine and natural product compounds. This effort focuses on small molecules contained in these libraries because small molecules are more likely to be efficacious drugs. Of the 10,000 synthetic compounds screened in 2005, 28 were found to disrupt microtubule function, and 10 of these have sufficient potency for consideration for further development. Dr. Brown's program at the University of Virginia is assisting with the design and synthesis of analogs that should have improved solubility without loss of antitumor activity.

Cardiovascular diseases

Atherosclerosis research. There is a considerable variability among individuals in the response of blood cholesterol levels to dietary fat and cholesterol content. On the basis of blood cholesterol responses to changes in dietary fat and cholesterol content, high- and low-responding individuals have been identified both within human subjects and animal species used to study cholesterol metabolism. High-responding individuals are at risk of developing atherosclerosis and other related cardiovascular diseases such as heart attack and stroke.

At SFBR, Dr. Rampratap Kushwaha's program uses baboon and laboratory opossum

models of diet-induced hyperlipidemia in an effort to identify the mechanisms that are responsible for determining whether an individual can be classified as a high or low responder to dietary fat and cholesterol. These studies in high- and low-responding baboons demonstrated that low-responding baboons have higher liver expression levels of an enzyme called 27-hydroxylase. They also have higher levels of transporters important in cholesterol absorption.

Metabolic studies conducted in high- and low-responding opossums found that liver metabolism of a plasma protein that binds cholesterol, low density lipoprotein apo B (LDL apo B), is increased in low responders. Together, these studies in baboons and opossums suggest that blood cholesterol levels are increased in high-responding individuals because their livers do not metabolize cholesterol as efficiently as low-responding individuals.

Dr. Henry C. McGill Jr., senior scientist emeritus at SFBR, in collaboration with the investigators involved in the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, continued to produce new findings in 2005. This study collected arteries, samples of blood and other tissues from persons between the ages of 15 and 35 years who died of external causes (e.g., car accidents) and underwent autopsies in forensic laboratories. Studies published in 2005 established that coronary artery atherosclerotic lesions were significantly increased by smoking in young individuals independently of other risk factors. Another study demonstrated that a biochemical marker of inflammation, C reactive protein, was also independently associated with increased coronary artery disease in young individuals.

Finally, in collaboration with Dr. Alex McMahan at the University of Texas Health Science Center at San Antonio, Dr. McGill and colleagues developed a scoring system based on coronary heart disease risk factors such as age, sex, serum lipoprotein levels, smoking, hypertension, obesity and hyperglycemia. The scoring system was designed to predict the probability of development of advanced coronary and aortic atherosclerotic lesions and was

2005 Doctoral Staff

(as of December)

Acting Chair
Robert E. Shade, Ph.D.

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

Scientist
Rampratap S. Kushwaha, Ph.D.

Associate Scientist
Susan Mooberry, Ph.D.

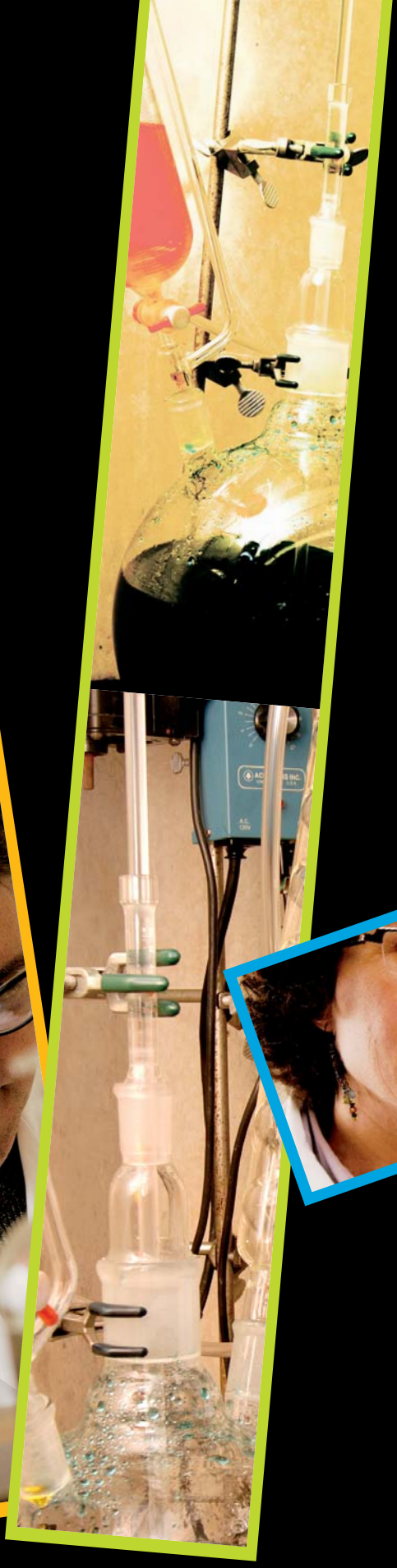
verified by comparison with the vascular lesion data in the PDAY study. As a result of this study, physicians now have a tool for identifying young individuals with a high probability of having advanced atherosclerotic lesions before these patients have developed symptoms of cardiovascular disease.

Hypertension research. In collaboration with Dr. Laura Cox in the SFBR Department of Genetics and Dr. J.R. Haywood at Michigan State University, Dr. Robert Shade is investigating the genetic mechanisms that contribute to hypertension that is exacerbated by dietary salt. This study uses a biochemical marker of cell membrane sodium transport, erythrocyte sodium-lithium countertransport (SLC), to identify baboons that are high or low for SLC. Humans with high SLC have been shown to have inherited salt-sensitive hypertension.

Preliminary results produced in 2005 have found that high dietary salt content increases blood pressure more in the high-SLC baboons, and these baboons experience a larger increase in blood pressure when given an infusion of a blood-pressure-raising hormone, angiotensin. Gene-expression studies conducted by Dr. Cox have identified 23 hypertension-related genes that are differentially expressed between high- and low-SLC baboons. One of the major goals of this study is to develop methods for identifying individuals at risk for developing salt-sensitive hypertension later in life, and to do so at a time when strategies can be developed to prevent the hypertension.

department of

organic chemistry



In April 2005, the Department of Organic Chemistry entered into year four of a five-year contract as The Synthetic Chemical Facility for the Contraceptive Development Branch (CDB) of the National Institute of Child Health and Human Development, National Institutes of Health. This marks the 29th consecutive year that the department has served in this capacity through a number of contracts.

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

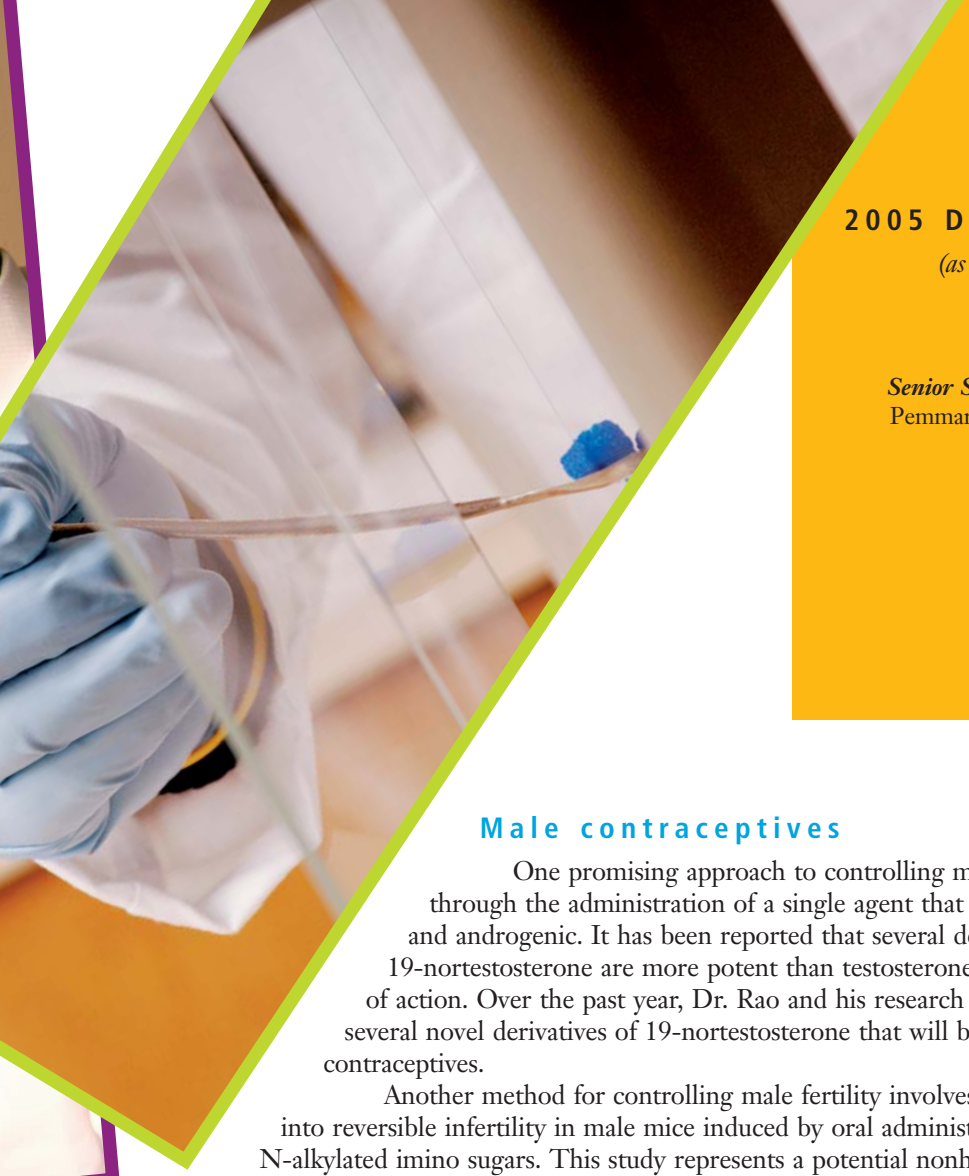
The department's current projects and areas of interest are highlighted below.

Selective progesterone receptor modulators

The potential applications of selective progesterone receptor modulators include contraception as well as treatment of endometriosis, progesterone dependent tumors, uterine fibroids, premenstrual syndrome and adverse symptoms of menopause. The antiprogestin known as CDB-4124 was conceived and synthesized in Dr. Rao's laboratories. Subsequent

biological testing indicated this analog exhibited three times the antiprogestational activity of the parent compound with significantly decreased side effects. This compound and 48 other derivatives are the subject of two U.S. patents awarded to scientists in the Department of Organic Chemistry in 2005.

Under the trade name Proellex™ (formerly known as Progenta™), CDB-4124 has been licensed to Zonagen Inc. for development in the treatment of uterine fibroids, endometriosis and progesterone-dependent breast tumors. In late 2004, Zonagen Inc. completed a European Phase Ib clinical study of Proellex™ in women with uterine fibroids. Results released by Zonagen Inc. in 2005 indicate that Proellex™ is well tolerated with no undue side effects and that women taking the drug achieved statistically significant reductions in fibroid size compared to a control group. Proellex™ also performed favorably when compared to a positive control group using Lupron®, a GnRH agonist commonly administered for the treatment of fibroids. In late 2005, Zonagen Inc. received approval to initiate a U.S. Phase 2 trial for the study of Proellex™ in the treatment of uterine fibroids, as well as approval to start a European Phase 2 study of Proellex™ for the treatment of endometriosis.



2005 Doctoral Staff

(as of December)

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

Male contraceptives

One promising approach to controlling male fertility is through the administration of a single agent that is both antigonadotropic and androgenic. It has been reported that several derivatives of 19-nortestosterone are more potent than testosterone with a longer duration of action. Over the past year, Dr. Rao and his research team have synthesized several novel derivatives of 19-nortestosterone that will be tested as male contraceptives.

Another method for controlling male fertility involves a recent investigation into reversible infertility in male mice induced by oral administration of certain N-alkylated imino sugars. This study represents a potential nonhormonal approach to male contraception. Over the past year, the department has synthesized two N-alkylated imino sugars to be studied by the National Institutes of Health in animal models.

Novel 2-methoxyestradiol compounds with cancer-fighting activity

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

The compounds and methods developed in Dr. Rao's laboratories for the synthesis of these analogs are the subject of two U.S. patents awarded to Southwest Foundation for Biomedical Research.

Over the past year, the Department of Organic Chemistry has synthesized several new analogs of 2-ME2 that have been tested by Entremed Inc. of Rockville, Md. Preliminary results from *in vitro* testing indicate five new compounds with promising results, one of which, known as RC-57, will be tested in an animal model by Entremed Inc.

southwest national

primate research center

The Southwest National Primate Research Center (SNPRC) continues to grow, taking on an ever-increasing role as a resource for investigators nationwide who rely on nonhuman primates for studies on human health and disease.

In 2005, the SNPRC supported the research efforts of 201 investigators, 70 percent of whom were located at institutions other than SFBR. Collaborators included major biomedical research institutions within Texas, such as Baylor College of Medicine, the University of Texas Medical Branch at Galveston, and the University of Texas Health Science Center at San Antonio, as well as top research institutions throughout the country, such as Harvard University, Stanford University, Brown University and the Salk Institute.

The breadth of research supported by the SNPRC is equally impressive. SNPRC resources, including animals and unique technical expertise, played a vital role in the study of atherosclerosis, hypertension, obesity, diabetes, prenatal and neonatal disease, aging, hepatitis C, bioterrorism threats, and HIV/AIDS.

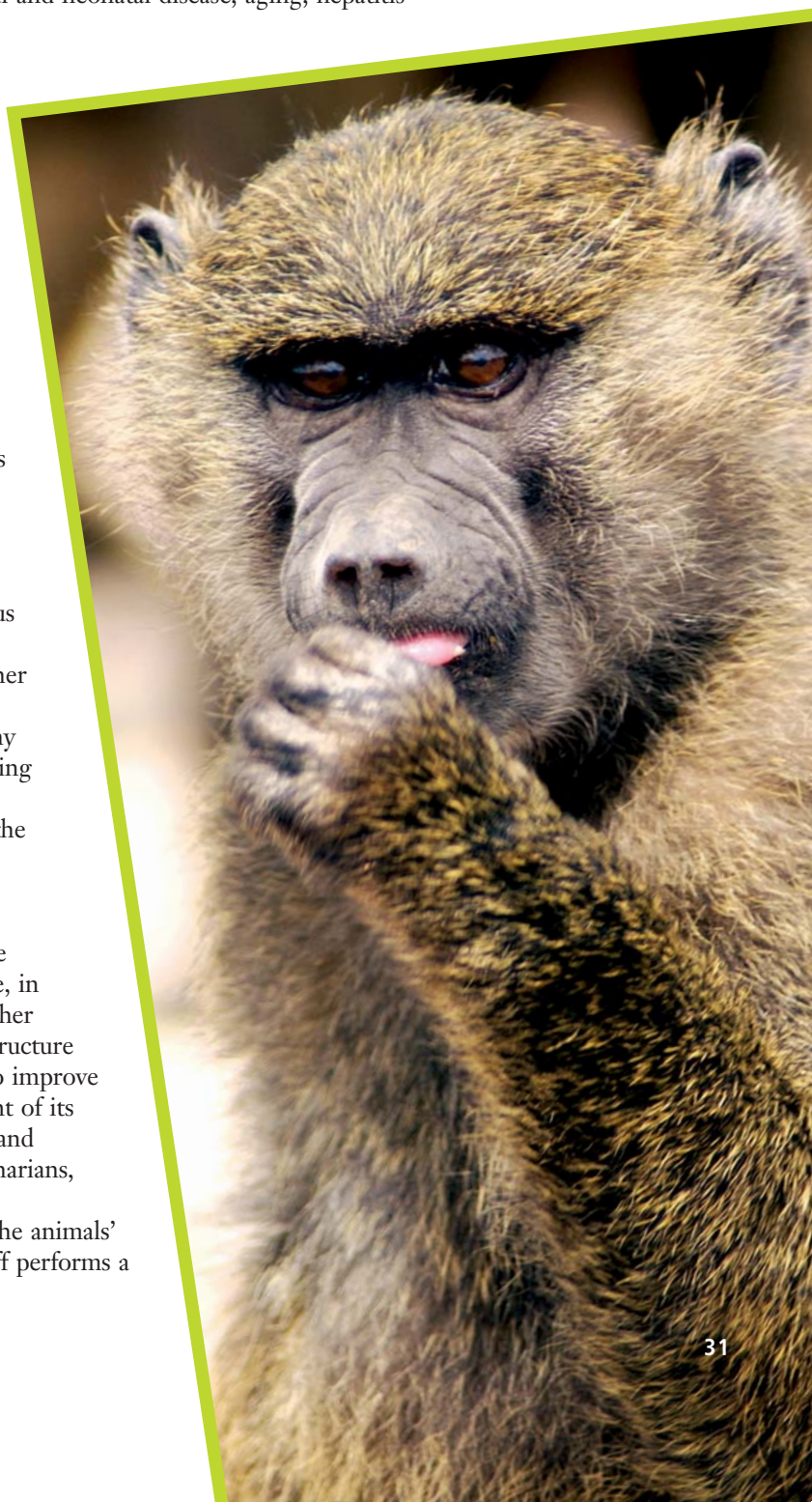
Mission and resources

These vital research collaborations are in keeping with the SNPRC's mission as one of eight National Primate Research Centers funded by the National Center for Research Resources, a division of the National Institutes of Health. Building upon SFBR's long and distinguished history in the appropriate care and use of nonhuman primates in research, the SNPRC was established in 1999 so that its unique combination of resources, infrastructure, animals and expertise could be better utilized by scientists at SFBR and throughout the United States as they strive for research advances to benefit human health.

The SNPRC's nonhuman primate colonies, which total nearly 6,000 animals, include more than 3,850 baboons, 1,350 cynomolgus macaques, 450 rhesus macaques, 200 chimpanzees, and 150 common marmosets, as well as a small number of animals of other species. These animals are critical to national research efforts due to the complexity of disease processes. Many investigations rely on the detailed study of a whole, living system, and as the animals most similar to humans in genetics and physiology, nonhuman primates serve as the gold standard for research in this area.

Historically, the SFBR's nonhuman primate resources have been managed as part of numerous departments within the foundation, coalescing into one department, the Department of Comparative Medicine, in 2003. In February 2006, the decision was made to further consolidate these resources under the administrative structure of the primate center. This restructuring is intended to improve the Foundation's efficiency in the care and management of its animal colonies, an effort that requires the dedication and expertise of a large and highly qualified team of veterinarians, veterinary technicians and animal care staff.

In addition to meeting the daily demands of the animals' physical care and enrichment needs, the veterinary staff performs a



wide variety of observational procedures and research protocols in support of research projects by SFBR and other collaborating scientists. The group also conducts research concerned with health problems in nonhuman primate colonies and searches for spontaneous nonhuman primate models of human disease.

A critical function of SNPRC staff is to ensure that all the Foundation's animal programs are in compliance with state and national regulations, federal regulatory agencies, and voluntary accrediting agencies. Since 1973, SFBR has voluntarily been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC, Int.), an agency that assures high-quality standards for the care and use of laboratory animals.

Supporting SFBR investigators in groundbreaking findings

The SNPRC has provided resources that formed the base of many of the most exciting research discoveries of SFBR scientists during 2005. In the Department of Virology and Immunology, for example, advancements in our understanding of and our ability to combat AIDS, hepatitis, and bioterror threats depended upon SNPRC resources. Specific examples include:

Verifying the authenticity of a new hepatitis C viral strain that, for the first time, can be tested in tissue culture. Hepatitis C virus (HCV), dubbed the "silent epidemic" because infected individuals can go for years without showing symptoms of disease, is the leading cause for liver transplantation. Likewise, liver cancer due to HCV infection is the most rapidly increasing form of cancer in the United States. There is no effective vaccine to protect against HCV infection, and current treatment regimens, which are extremely difficult on patients, are effective only 50 percent of the time. While an obvious need exists for a vaccine and new drug therapies against HCV, until now, research efforts in this area have been hampered by the inability to test candidate vaccines and drug treatments against hepatitis C virus grown in tissue culture in the laboratory.

In 2005, Dr. Charles Rice at Rockefeller University in New York developed a special strain of HCV that replicates in tissue culture. This was a major advance in the field. Replication in tissue culture has long been considered the "Holy Grail" for HCV research. However, there was still considerable concern that, having grown in tissue culture, the viral strain may have mutated or altered itself in such a way that it would no longer replicate in the

liver of humans or chimpanzees and cause hepatitis, in which case it would not be an authentic representation of the virus. Problems have occurred in the past when drugs were designed to inhibit virus replication in tissue culture and then failed to work in the clinic, because the virus in man differs from the virus that has adapted to replicate in culture.

To validate the authenticity of this special strain of HCV, Dr. Robert Lanford, a scientist with the SFBR Department of Virology and Immunology and with the SNPRC, along with the scientist at Rockefeller University, inoculated the virus grown in culture into chimpanzees. Chimpanzees are the only animals besides humans that are susceptible to HCV infection, but unlike humans, they do not develop liver disease from the infection, making them particularly valuable to these types of studies. The results demonstrated that the new viral strain replicates *in vivo* in the liver and causes hepatitis. In subsequent tests, virus from the chimpanzee was reintroduced into tissue culture systems in the laboratory, where it again replicated successfully. This completed the full circle from tissue culture to animal and back to tissue culture.

Thus, for the first time, pharmaceutical companies and other researchers have a validated culture system to test potential HCV treatments and vaccines in the laboratory. In addition to the expected benefit to human health, this finding also should reduce the number of animals needed in HCV research, since some investigations that formerly could be done only with chimpanzees can now be conducted in tissue culture.

Development of a new animal model of Lassa fever virus infection. As scientists search for vaccines and therapies against potential bioterror agents, the development of nonhuman primate models for the study of these pathogens is critical. Because these pathogens are infrequently encountered in nature, and because it would be unethical to deliberately expose people to them for research studies, it is not feasible to test potential new medications for efficacy in humans. Therefore, the Food and Drug Administration has enacted the "two animal rule" for approval of new drugs to prevent or treat diseases caused by select agents, or pathogens considered by the federal government to be possible agents of bioterror. If a new vaccine or therapy proves to be safe and effective in two animal models, it can be approved by the FDA for use in humans and stockpiled in case of a national emergency. Because nonhuman primates are the animals most similar to humans in genetics and physiology, and therefore their response to both the pathogens and potential treatments would be most like our own, it is preferable that they serve as one of the two animal models used in these research trials.

The smallest-bodied primates are desirable as subjects in studies that require the highest levels of biocontainment. For this reason, scientists at SFBR and the SNPRC have been working to develop the marmoset monkey as a research model for various select agents, including Lassa hemorrhagic fever. In 2005, marmosets were subcutaneously inoculated with Lassa Josiah (an Old World hemorrhagic fever virus) in the maximum containment facility

at the SNPRC's host institution, SFBR, in an attempt to determine whether this small, New World primate could serve as a model for Old World hemorrhagic fever infections. By the fourth day, they detected the virus in the blood and in all tissues of the inoculated animals. Likewise, the course of infection was consistent with that of other Lassa hemorrhagic fever models. Elevated replication in the spleen, adrenals, liver and lymph nodes was similar to Lassa infection in humans, as was histopathology. These findings suggest that the marmoset is a promising model of Lassa fever infection, and it will be used in the future to test vaccines against this potential bioterror agent.

An explanation for resistance to HIV and AIDS. Although chimpanzees can be infected with HIV, it is rare that infection in these animals leads to the development of AIDS, with its loss of CD4+ T immune cells, immunodeficiency and opportunistic infections. Likewise, some people show a stronger resistance than others to natural infection, and some who are infected with HIV progress to disease much more slowly than others. It is hoped that if scientists can determine what gives chimpanzees – and some people – their natural defense against AIDS, they may be able to develop a vaccine or new, more effective therapies based on that knowledge.

Recently, Dr. Krishna Murthy, an investigator with SFBR and the SNPRC, collaborated with researchers at the University of Texas Health Science Center at San Antonio on a comparative study that revealed a correlation between people's genetic susceptibility to HIV/AIDS and the number of copies they carry of a gene that codes for a protein known as CCL31 chemokine. This chemokine has potent suppressive activity against HIV, and study results showed that individuals carrying a lower number of copies of the gene showed increased susceptibility to HIV infection and subsequent progression to AIDS. On the other hand, a higher number of copies of the gene led to resistance to HIV infection and slower progression to disease. For example, two or more copies of the CCL31 gene were associated with resistance to rapid AIDS progression in humans.

A subsequent comparison with chimpanzees revealed that 95 percent of the animals carried 5 to 10 copies of the CCL3L1 gene, and the remaining 5 percent carried 11 to 17 copies. It is therefore believed that possession of higher copy numbers of CCL31 likely provides selective advantage to chimpanzees with regard to HIV and AIDS.

Enabling vital national research efforts

Just one example of an area in which SNPRC resources are a critical building block for national research efforts is the study of pregnancy and perinatal health and disease. With the largest baboon colony in the world and the recognized value of the baboon as a model in this area of study, SNPRC resources are critical to advancements in this area. In the past three years, for example, the SNPRC has provided the resources necessary for principal investigators from:

- ▷ The University of Texas at San Antonio in their investigations on:
  - The effects of maternal nutrition on pregnancy outcomes
  - Diseases of prematurity
- ▷ The University of Texas Medical Branch at Galveston and the University of Pittsburgh in their studies on:
  - The dynamics of common and new drugs used during pregnancy
- ▷ The University of Kentucky and the University of Texas Health Science Center at San Antonio in research on:
  - The effects of periodontal disease during pregnancy on preterm birth
- ▷ The University of Maryland and its investigations on:
  - The establishment of pregnancy and how this process goes awry
- ▷ Stanford University:
  - Perfecting techniques for fetal surgery

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sfbr 2005

scientific publications

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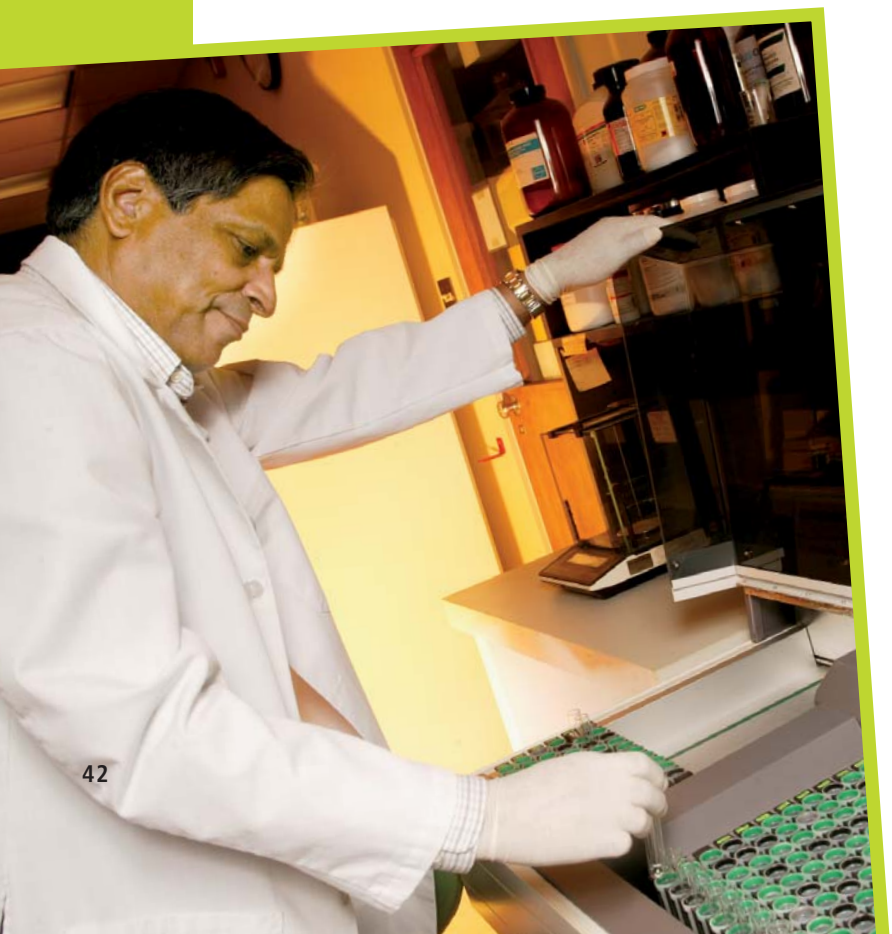

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Advancing science through education:

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

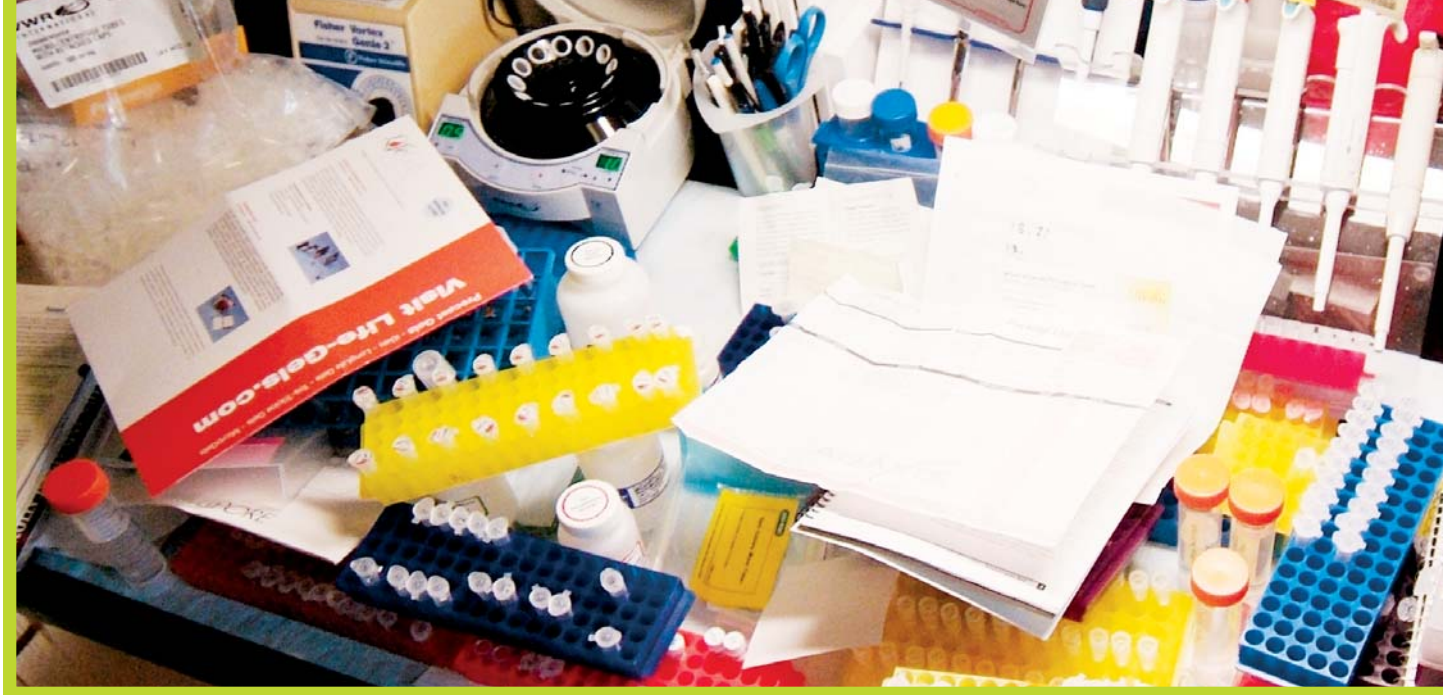
Conferences and workshops sponsored in 2005

2nd International Congress on the Future of Animal Research
Date: August 16-19, 2005
Location: Rio de Janeiro, Brazil

Organized by an international team of scientists and veterinarians under the leadership of Dr. John VandeBerg, who chaired both the International Committee and the Executive Committee, the meeting had several objectives: to bring together laboratory animal scientists and veterinarians from around the world to discuss current trends in research with animals, as well as alternatives; to develop a collective vision of future opportunities; to foster the international harmonization of standards in the care and use of animals; and to establish international collaborative opportunities for established scientists as well as students and postdoctoral fellows. In addition to SFBR, sponsoring institutions included; FIOCRUZ, Rio de Janeiro, Brazil; COBEA, Sao Paulo, Brazil; and ABMA, Rio de Janeiro, Brazil. The following contributors helped make the meeting possible: The Newman Family Charitable Trust of the San Antonio Area Foundation; The Robert J. Kleberg Jr. and Helen C. Kleberg Foundation; Alesco Indústria e Comércio Ltda.; Alsco – Toalheiro Brasil Ltda.; Beiramar Indústria e Comércio Ltda.; Conselho Regional de Medicina Veterinaria do Rio de Janeiro; Hemoin Productos para Biotérios Ltda.; Nuvital Nutrientes S.A.; Sogorb Indústria e Comércio Ltda.

Anthropological and Primate Genetics Workshop
Date: December 8-10, 2005
Location: Southwest Foundation for Biomedical Research, San Antonio, Texas

The American Association of Anthropological Genetics and the Southwest Foundation for Biomedical Research teamed up to sponsor this workshop, which focused on the study of normal variation and genetic epidemiology in both human and nonhuman primates. Presenters introduced concepts, methods, and results of genetic analysis with the aim of helping participants design their own genetic studies. The workshop was intended for graduate students and faculty interested in integrating various genetic methods into their research programs, but it also was open to advanced undergraduates and others with a serious interest in these types of analyses. Dr. Lorena Havill, staff scientist in the Department of Genetics, chaired this informative and well-attended event with the help of Dr. Deidre Winnier, a postdoctoral scientist with the department. The workshop was made possible through the generous sponsorship of several organizations: Applied Biosystems; Illumina, Inc.; M&A Technology; Purina Mills, Inc.; Sigma Solutions; and Fisher Scientific Company, L.L.C.



SFBR Faculty Seminar Series

Throughout the year, the Southwest Foundation for Biomedical Research hosts a series of seminars featuring scientific experts from its own faculty as well as other top researchers from across the United States, who present information about their latest efforts and findings in the search for new ways to fight diseases of every kind. SFBR makes this seminar series open to the public to help meet the continuing education needs of scientists at its peer research institutions throughout the local community. A note of thanks goes to Dr. Tim Anderson, assistant scientist in the Department of Genetics, who organized the following programs in 2005.

Signal Transduction Mechanisms in Memory Formation
January 20, 2005
Presented by David Sweatt, Ph.D.
Adjunct Professor, Department of Neuroscience
Baylor College of Medicine

Identification of Diabesity Genes on Chromosome 6 in Mexican Americans
March 3, 2005
Presented by Chris Jenkinson, Ph.D.
Associate Professor, Diabetes Division
Director, Molecular Genetics Core
Department of Medicine
The University of Texas Health Science Center
at San Antonio

The Chimpanzee Model of Hepatitis C
April 7, 2005
Presented by Robert Lanford, Ph.D.
Scientist, Department of Virology and Immunology
Southwest Foundation for Biomedical Research

Systematic Approaches to the Study of Functional Polymorphism: The -308 Promoter SNP of the TNF Gene
June 2, 2005
Presented by Lawrence J. Abraham, Ph.D.
Associate Professor, Biochemistry and Molecular Biology
The University of Western Australia

Pathogenesis of Type 2 Diabetes Mellitus: Physiologic, Biochemical and Molecular Insights
July 7, 2005
Presented by Ralph A. DeFronzo, M.D.
Chief, Diabetes Division
Department of Medicine
The University of Texas Health Science Center
at San Antonio

Genomic Organization of the Growth Hormone Locus in Humans and Nonhuman Primates
August 4, 2005
Presented by Hugo Barrera, Ph.D.
Professor of Biochemistry
Universidad Autónoma de Nuevo León, Monterrey, Mexico

Continued on page 48

SFBR Faculty Seminar Series

Continued from page 47

Genetics of Osteoporosis: The Pedigreed Baboon Model
September 1, 2005
Presented by Lorena Havill, Ph.D.
Staff Scientist, Department of Genetics
Southwest Foundation for Biomedical Research

The Latest Advances in Biodefense Research at SFBR
October 6, 2005
Presented by Ricardo Carrion Jr., Ph.D.
Staff Scientist, Department of Virology and Immunology
Southwest Foundation for Biomedical Research

Use of the Norfolk Island Genetic Isolate for Complex Disease Gene Mapping
October 31, 2005
Presented by Lyn Griffiths, Ph.D.
Director, Genomics Research Centre
Head, School of Medical Science
Griffith University, Australia

T Cell Receptor Repertoire Development in Health and Disease
November 3, 2005
Presented by Anthony J. Infante, M.D., Ph.D.
President, Southwest Foundation for Biomedical Research

Dissecting Gene Expression Regulation with RNA Binding Proteins
December 1, 2005
Presented by Luiz Penalva, Ph.D.
Assistant Professor of Cellular and Structural Biology
Children's Cancer Research Institute
The University of Texas Health Science Center at San Antonio

New Grants and Contracts Awarded in 2005

Federal Research Grants and Contracts

	Length of Grant	Total Amount to SFBR
NIH *Genetics of Coronary Artery Disease in Alaska Natives* Dr. Jean MacCluer, principal investigator	5 years	$ 3,484,374
NIH *TB Vaccine Development in Nonhuman Primate Model* Dr. John VandeBerg, principal investigator	5 years	$ 3,442,487
NIH *A Genome Scan for Susceptibility to Helminthic Infection* Dr. Sarah Williams-Blangero, principal investigator	5 years	$ 3,067,201
NIH *The Metabolic Syndrome in Mexican American Children* Dr. Ravindranath Duggirala, principal investigator	5 years	$ 2,311,584
NIH *Toward a Molecular-Defined Vaccine for Schistosomiasis* Dr. Philip LoVerde, principal investigator	5 years	$ 1,860,854
NIH *Genetic Linkage Mapping in Rhesus Monkeys* Dr. Jeff Rogers, principal investigator	4 years	$ 1,513,506
NIH *Southwest National Primate Research Center – supplement* Dr. Anthony Infante, principal investigator Dr. John VandeBerg, director	9 months	$ 1,217,959
CDC *Safety, Immunogenicity and Efficacy of WNV and Other Flavivirus DNA Vaccine Candidates* Dr. Jean Patterson, principal investigator	2 years	$ 1,027,809
NIH *Strong Heart Family Study — bridge funding* Dr. Jean MacCluer, principal investigator	2 months	$ 995,475
NIH *Genetic Analysis of Osteoporosis Risk Factor* Dr. Stefan Czerwinski, Wright State University, principal investigator; Dr. John Blangero, principal investigator on subcontract to SFBR	5 years	$ 907,263

Continued on page 50

	Length of Grant	Total Amount to SFBR
NIH *HCV Replication and Immunity in Chimpanzees* Dr. Christopher Walker, Ohio State University, principal investigator; Dr. Krishna Murthy, principal investigator on subcontract to SFBR	4 years	$ 850,711
NIH *Improving Safety and Efficacy of Gene Therapy with HDAd* Dr. Philip Ng, Baylor College of Medicine, principal investigator; Dr. K. Dee Carey, principal investigator on subcontract to SFBR	5 years	$ 601,444
NIH *Training in Emerging and Re-emerging Diseases in Brazil* Dr. Philip LoVerde, principal investigator	3 years	$ 470,744
NIH *Genetics of Opioid Dependence* Dr. Joel Gelernter, Yale University, principal investigator; Dr. Laura Almasy, principal investigator on subcontract to SFBR	5 years	$ 381,943
NIH *Establishment of an SPF Rhesus Macaque Colony – bridge funding* Dr. Larry B. Cummins, principal investigator	7 months	$ 354,478
NIH *Development of a Recombinant Subunit Vaccine for the Prevention of West Nile Virus Infection in Humans* Dr. Michael Lieberman, Hawaii Biotech, Inc., principal investigator; Dr. Karen Rice, principal investigator on subcontract to SFBR	9 months	$ 319,557
NIH *Genetics of Bipolar Disorder in Latino Populations* Dr. Michael Escamilla, University of Texas Health Science Center at San Antonio, principal investigator; Dr. Laura Almasy, principal investigator on subcontract to SFBR	5 years	$ 284,840
Department of Defense *Foodborne Anthrax Threat Assessment* Dr. Jean Patterson, principal investigator	10 months	$ 217,413
Naval Research Laboratory *Development and Testing of Recombinant Single Domain Antibodies* Dr. Andrew Hayhurst, principal investigator	1 year	$ 149,870
NIH *Genetic Architecture of the Baboon Craniofacial Complex* Dr. Richard Sherwood, Wright State University, principal investigator; Dr. Michael Mahaney, principal investigator on subcontract to SFBR	2 years	$ 146,422
NIH *Mopeia/Lassa Chimeric Vaccine Against Lassa Fever* Dr. Igor Lukashevich, University of Maryland Biotechnology Institute, principal investigator; Dr. Jean Patterson, principal investigator on subcontract to SFBR	1 year	$ 140,600

	Length of Grant	Total Amount to SFBR
NIH *Development of Hepatitis C Virus-Like Particles as a Candidate HCV Vaccine* Dr. Krishna Murthy, principal investigator	1 year	$ 134,730
NIH *Genetics of Atherosclerosis in Mexican Americans – supplement* Dr. Jean MacCluer, principal investigator	2 years	$ 124,484
NIH *Obstetric-Fetal Pharmacology Research Units Network – supplement* Dr. Gary Hankins, University of Texas Medical Branch at Galveston, principal investigator; Dr. K. Dee Carey, principal investigator on subcontract to SFBR	4 months	$ 117,952
Miscellaneous federal grants and contracts (under $100,000 each)		$ 907,819
Total Federal Research Grants and Contracts		**$ 25,031,519**

Commercial Research Contracts

Department of Comparative Medicine (33)	$ 5,152,387
Department of Virology and Immunology (9)	$ 452,673
Department of Genetics (2)	$ 12,844
Total Commercial Research Contracts	**$ 5,617,904**

Research Grants from Philanthropic Donors

Richard and Dianne Azar Fund *Genetic Dissection of Cystinosis: An Innovative Program for Novel Mechanism/Gene Discovery* Dr. John Blangero, principal investigator	1 year	$ 985,875
Robert J. Kleberg Jr. and Helen C. Kleberg Foundation *Monodelphis Research Program – supplement* Dr. John VandeBerg, principal investigator	1 year	$ 368,000
Raymond Dickson Foundation *Library Electronic Classroom – supplement*	2 years	$ 100,000
Southwest Foundation Forum *Screening of CD36 as a Positional Candidate Gene for Metabolic Syndrome* Dr. Vidya Farook, principal investigator	1 year	$ 25,000
Southwest Foundation Forum *Quantitative Trait Nucleotide Analysis of Positional Candidate Genes for Circulating Levels of Inflammatory Marker ICAM-1* Dr. Jack Kent Jr., principal investigator	1 year	$ 24,705

Continued on page 52

Southwest Foundation Forum *Genetics of Preeclampsia/Eclampsia in the Jirel Population of Eastern Nepal* Dr. Eric Moses, principal investigator	1 year	$	24,522
Southwest Foundation Forum *A Comprehensive Dissection of PSARI, a Positional Candidate Gene for Diabetes Susceptibility* Dr. Joanne Curran, principal investigator	1 year	$	23,892
Joe and Jesse Crump Foundation *Cancer Drug Development – supplement* Dr. Susan Mooberry, principal investigator	6 months	$	20,000
Joe and Jesse Crump Foundation *Cancer Drug Development – supplement* Dr. Susan Mooberry, principal investigator	4 months	$	20,000
San Antonio Area Foundation *Identifying Genetic Effects on Bone Microstructure Related to Osteoporosis Risk Using a Baboon Model* Dr. Lorena Havill, principal investigator	1 year	$	14,589
Shelby Rae Tengg Foundation *Identification of New Taccalonolides – supplement* Dr. Susan Mooberry, principal investigator	11 months	$	10,000
Total Philanthropic Grants[i]		**$**	**1,616,583**
Total of New Grants and Contracts Awarded During 2005		**$**	**32,266,006**

[i]Additional philanthropic grants were utilized to fund the construction of the Ledford Building on the SFBR campus and to provide start-up funds for the laboratory of Dr. Philip T. LoVerde. Some of the following grants were awarded in previous years, but all were expended in 2005.

Granting Organization	Total Amount to SFBR
USAA Foundation	$ 1,050,000
Elizabeth Huth Coates Foundation	$ 500,000
Helen Storey Estate	$ 250,000
Ewing Halsell Foundation	$ 220,000
Gorman Foundation	$ 100,000
Brown Foundation	$ 100,000
Amy Shelton McNutt Foundation	$ 5,000
Southwest Foundation Forum	$ 3,000

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 85 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, the neonatal intensive care research 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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