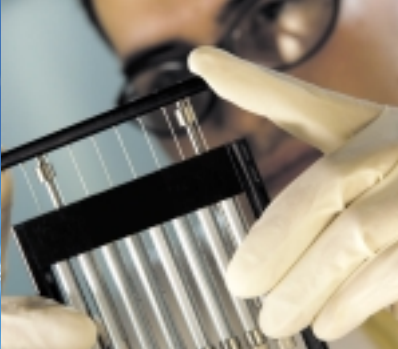




SFBR

southwest foundation for biomedical research



2002
report of
progress



reaching new
heights





reaching new heights

for more than 60 years, scientists at the Southwest Foundation for Biomedical Research have devoted themselves to the race for discovery, striving to find the answers to the never-ending list of questions about the maladies that plague our world. Currently, the Foundation has more than 70 doctoral-level scientists leading nearly 180 major research projects targeting such health concerns as heart disease, diabetes, obesity, cancer, AIDS, hepatitis, premature lung disease, osteoporosis, psychiatric disorders, malaria, parasitic infections, and a host of other infectious diseases.

Although their work can be painstakingly tedious, SFBR scientists continue each year to push themselves to reach new heights and achieve a greater level of progress. Consequently, in their efforts to identify new ways to attack and prevent disease, they often find themselves at the forefront of biomedical research.

The 2002 year proved to be another pace-setter, as the Foundation once again set new records in scientific progress. One measure of this progress is the amount of new grants and contracts awarded to Foundation scientists.

As the following pages explain, 2002 was the sixth consecutive year of record-setting grant awards, a true compliment to the quality of research carried out by SFBR faculty.

Of course, those grants are all geared toward improving human health, and in this area, Foundation researchers have continued to shine as well. A sampling of their major scientific accomplishments is described in the pages ahead, with a more complete overview provided in the departmental reports.



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

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

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

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

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

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



letter from the president

during my 11 years at the helm of this organization, I have seen tremendous growth: growth in the achievements of our faculty, growth in our campus, and growth in the support we enjoy from our many friends and benefactors. In all of these areas, I am happy to say that 2002 was an extraordinary year.

One important way we measure our growth at the Foundation is by the amount of new grants and contracts we receive. Here, 2002 broke all records. As you will see in the following pages, our scientists were awarded \$45.8 million in new grants and contracts during 2002, up from \$35.38 million just the year before and from \$22.9 million in 1997. This equates to a 28 percent increase in one year's time and a doubling of awards within a five-year period.

This is truly outstanding, especially considering that our number of faculty has remained relatively constant. And while it speaks volumes about our scientists' productivity, it also acclaims the quality of their research, since the vast majority of those awards are based on peer review.

I hope you will take some time to review the scientific reports in this publication, because they tell us what these grants actually mean to human health. Whether their work focuses on cardiovascular disease, infectious diseases such as AIDS or hepatitis, emerging viruses, biodefense, diabetes, psychiatric disorders, cancer, maternal and child health, premature lung disease or problems associated with aging, our scientists are ever advancing in their quest for new understandings that might lead to improved methods of treatment or prevention.

Our efforts to rebuild our campus are designed to assist our scientists in these important endeavors. Currently, SFBR is undergoing the most extensive campus remodeling and renovation program in its history, with 19 construction projects either underway or in various stages of planning. Many of these programs are aimed at rebuilding current structures or adding new facilities to provide quality housing and care for our animal colony, which is invaluable to our

scientific research. In addition, we have several major laboratory projects that are about to come online.

One exciting new project has just been completed as I write this report. On June 18, 2003, we held the grand opening of our new SBC Genomics Computing Center, which contains the world's largest computer cluster devoted to statistical genetics research. With its tremendous computing capability, this unique asset will dramatically increase the speed with which our scientists search for genes influencing many of life's most pressing diseases. Complicated analyses that once took weeks or even months to compute can now be completed in mere minutes. What a fabulous application of technology to solve real human health problems.

The campus renovation I have described is heavily dependent upon community support, and here the Foundation has seen growth as well. While we are still in the midst of a \$40.3 million capital campaign to help us fund new laboratories, recruit outstanding new faculty, and build up our endowment, that campaign already has generated over \$36 million in gifts. I am especially pleased to report that in the past year SFBR was the beneficiary of two multi-million-dollar estates, which should greatly assist the forward progress of the Foundation.

I want to thank the many dedicated friends of SFBR who understand that philanthropic donations have given us the opportunity to advance both in our scientific programs and in the laboratories and facilities that allow our scientists to excel. Through your support, you make our work your own. With this in mind, the following *Report of Progress* is not only a tribute to the fine work of our scientists, but to you as well.

Respectfully submitted,

Frank F. Ledford, Jr., MD, FACS
President



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SFBR Sees Record Year in New Grants and Contracts

Awards Double in Five-Year Period

SFBR is fortunate to have not only some of the brightest but also some of the most productive scientists in the nation, continually pushing themselves to achieve more in their effort to advance scientific understanding and improve human health. A visible indicator of their success is the rate at which they are increasing new research grants and contracts to the Foundation.

In 2002, the Foundation saw another record-setting year, with new grants and contracts totaling more than \$45.8 million. This is more than a \$10 million – or 28 percent – increase over the previous year’s awards, which totaled \$35.38 million.

Not only does this mark the sixth consecutive year of record-setting grant awards to SFBR, which has seen totals rise steadily since 1997, but it also shows a doubling of the organization’s awards during that same time period. New grants and contracts totaled \$22.9 million in 1997 compared to 2002’s \$45.8 million.

“This speaks volumes about the dedication of our scientists and the quality of their work,” said Dr. Frank Ledford, SFBR president. “While the number of our scientific faculty has remained fairly constant over the past several years, our new grants and contracts have continued to rise to the point where they have doubled in half a decade. In addition, since the majority of these grants are awarded from the National Institutes of Health (NIH), which judges applications by peer review, we know that scientists around the country recognize the outstanding quality of our faculty’s research.”

The 24 NIH grants ranged in size from \$11.6 million to study the genetics of atherosclerosis in Mexican Americans to \$130,708 for comparative genomic analysis of cardiovascular genes. Topics of research also covered a broad spectrum, including HIV/AIDS, salt-sensitive hypertension, diabetes, idiopathic thrombosis, mental illness, hepatitis C, gall bladder disease, and child birth-weight, growth, and development. NIH also granted more than \$3 million to help upgrade the Foundation’s animal facilities.

Contracts with private industry and other government agencies made up the next largest portion of the new awards, followed by grants from philanthropic groups. Organizations such as the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation, the William Randolph Hearst Foundation, the Amon G. Carter Foundation, the Minnie Stevens Piper Foundation and the San Antonio Area Foundation helped sponsor research on cancer, diseases of neonatal infants, and the repair of spinal cord injury.

Many of these new grants and contracts are multi-year awards, with actual funding spread out over the term of their related projects. Therefore, they will positively impact SFBR’s budget for years to come.

This is made evident by a look at SFBR’s recent history. Between 1998 and 2002, the Foundation’s annual budget grew from \$27.2 million to \$48.8 million. That fast-paced growth is attributed to



record-setting grant awards, an increase in construction projects to accommodate the Foundation's scientific growth, and donor generosity.

While approximately 75 percent of SFBR's budget is met through competitive grants and contracts, the organization depends on philanthropic support to fund new research initiatives, construction expenses, and other vital projects that cannot be supported with grant funding. The local community has been generous with the Foundation since its earliest days – most recently contributing more than \$36 million towards its \$40.3 million capital campaign – and that support is necessary to ensure continued growth and scientific achievement at SFBR in future years.

National Institutes of Health (NIH) Funds SFBR's Top Five Grant Awards in 2002

1. "Genetics of Atherosclerosis in Mexican Americans" – a genetic study of heart disease, diabetes and obesity in the Mexican American population, \$11.6 million. (Dr. Jean MacCluer, Department of Genetics, principal investigator)
2. "Maintenance and Operation of a Synthetic Chemical Facility" – a study of synthetic hormones for cancer therapy and reproductive medicine, \$6.2 million. (Dr. P.N. Rao, Department of Organic Chemistry, principal investigator)
3. "Determinants of Natural Host Resistance to SIVagm" – a study of the African green monkey's natural resistance to immunodeficiency viruses, \$2.6 million (Dr. Jonathan Allan, Department of Virology and Immunology, principal investigator)
4. "Angiotensin, Sodium and Genes in Primate Hypertension" – a study on the genetics of salt-sensitive hypertension, \$2.1 million. (Dr. Robert Shade, scientific director and scientist in SFBR's Department of Physiology and Medicine, principal investigator)
5. "Genetics of Monoamine Endophenotypes and Mental Health" – a study on the genetics of



SFBR Financial Facts:

SFBR Sees Six Consecutive Years of Record Totals in New Grants and Contracts

1997:	\$22.9 million
1998:	\$23.7 million
1999:	\$29.2 million
2000:	\$31.0 million
2001:	\$35.4 million
2002:	\$45.8 million

SFBR's Annual Budget Sees Record Growth

1998:	\$27.2 million
1999:	\$29.8 million
2000:	\$35.5 million
2001:	\$39.1 million
2002:	\$48.8 million

biochemical markers for risk of mental disorders, \$1.9 million. (Dr. Jeffrey Rogers, Department of Genetics, principal investigator).

New Grants and Contracts Awarded in 2002

FEDERAL RESEARCH GRANTS

	Length of Grant	Total Amount to SFBR
<p>NIH <i>Genetics of Atherosclerosis in Mexican Americans</i> Dr. Jean MacCluer, principal investigator</p>	5 years	\$11,647,489
<p>NIH <i>Maintenance and Operation of a Synthetic Chemical Facility</i> Dr. P.N. Rao, principal investigator</p>	5 years	\$ 6,232,987
<p>NIH <i>Determinants of Natural Host Resistance to SIVagm</i> Dr. Jonathan Allan, principal investigator</p>	4 years	\$ 2,622,068
<p>NIH <i>Angiotensin, Sodium and Genes in Primate Hypertension</i> Dr. Robert Shade, principal investigator</p>	4 years	\$ 2,093,319
<p>NIH <i>Genetics of Monoamine Endophenotypes and Mental Health</i> Dr. Jeffrey Rogers, principal investigator</p>	5 years	\$ 1,980,000
<p>NIH <i>Genetic Analysis of Idiopathic Thrombosis</i> Dr. Laura Almasy, principal investigator</p>	4 years	\$ 1,847,366
<p>NIH <i>Genetics of Birth Weight in Mexican Americans</i> Dr. Ravindranath Duggirala, principal investigator</p>	4.5 years	\$ 1,781,183
<p>NIH <i>Molecular Mechanisms for HCMV Mediated Atherogenesis</i> Dr. Xing Li Wang, principal investigator</p>	4 years	\$ 1,760,000
<p>NIH <i>Molecular Genetic Markers in Primate Disease Models</i> Dr. Jeffrey Rogers, principal investigator</p>	4 years	\$ 1,232,000

Continued

NIH

Periodontitis and Preterm Birth: Nonhuman Primate Model
Dr. Jeffrey Ebersole, University of Kentucky, principal investigator/Dr. Larry B. Cummins, SFBR, co-investigator

Length of Grant

Total Amount to SFBR

5 years

\$ 1,194,328

NIH

Opossum Model for the High & Low Responses to Diet
Dr. Rampratap Kushwaha, principal investigator

3 years

\$ 1,079,389

NIH

Genetic and Environmental Influences on Childhood Growth
Dr. Bradford Towne, Wright State University, principal investigator/Dr. Sarah Williams-Blangero, SFBR, co-investigator

5 years

\$ 557,135

NIH

Genetics of Birth Weight in Mexican Americans
Dr. Ravindranath Duggirala, principal investigator

5 years

\$ 396,909

NIH: Office of AIDS Research

Southwest National Primate Research Center
Dr. Frank F. Ledford, Jr., principal investigator

1 year

\$ 385,000

NIH

Application of Transgenic Technologies to Baboons
Dr. John McCarrey, principal investigator

2 years

\$ 352,000

NIH

Genetics of Gallbladder Disease in Mexican Americans
Dr. Ravindranath Duggirala, principal investigator

1 year

\$ 293,822

NIH

Mapping Drug Resistance Genes in Plasmodium falciparum
Dr. Timothy Anderson, principal investigator

4 years

\$ 276,172

NIH

HIV-1 Adenovirus-Based Vaccine Study in Chimpanzees
Dr. Krishna Murthy, principal investigator

1 year

\$ 275,782

NIH

Unix Computer Cluster
Dr. Bennett Dyke, principal investigator

1 year

\$ 228,214



Continued

NIH

Chimeric Virus Primate Model of Hepatitis C
 Dr. Stanley Lemon, UTMB-Galveston, principal investigator/
 Dr. Robert Lanford, SFBR, co-investigator

Length of Grant

4 years

Total Amount to SFBR

\$ 211,727

USAF

Force Protection Battlelab Military Working Dog
 Biological Organism Search Study (K-9 Boss) Phase II
 Dr. Jean Patterson, principal investigator

6 months

\$ 191,696

FDA

Assessment of HCV Vaccines in Chimps
 Dr. Thomas Butler, principal investigator

1 year

\$ 150,000

NIH

Comparative Genomic Analysis of Cardiovascular Gene
 Dr. Anthony Comuzzie, principal investigator

2 years

\$ 130,708

NIH

Southwest National Primate Research Center, Supplement for
Transportation and Maintenance of 14 Chimpanzees
 Dr. Frank F. Ledford, Jr., principal investigator

1 year

\$ 109,688

TOTAL FEDERAL RESEARCH GRANTS

\$37,028,982



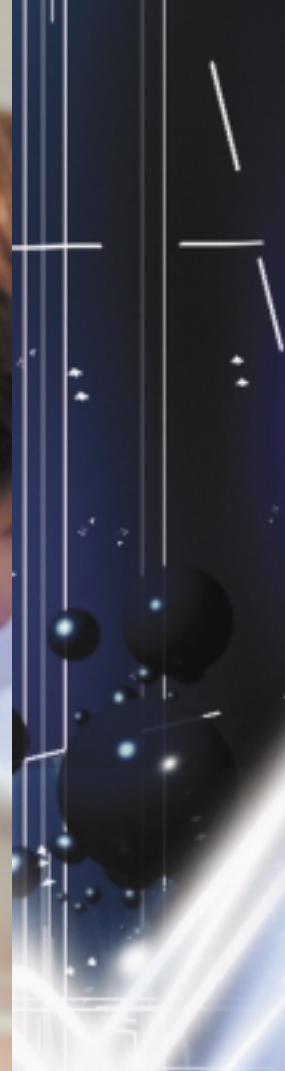
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RESEARCH GRANTS FROM PHILANTHROPIC DONORS

	Length of Grant	Total Amount to SFBR
<p>Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation <i>Monodelphis Research Program</i> Dr. John VandeBerg, principal investigator</p>	1 year	\$ 326,000
<p>William Randolph Hearst Foundation <i>Cancer Drug Discovery Program:</i> <i>New Microtubule-Disrupting Agents and Antiangiogenic Agents</i> Dr. Susan Mooberry, principal investigator</p>	2 years	\$ 250,000
<p>Amon G. Carter Foundation <i>Cancer Drug Development Program</i> Dr. Susan Mooberry, principal investigator</p>	1 year	\$ 100,000
<p>Miscellaneous:</p>		\$ 111,500
<p>TOTAL PHILANTHROPIC GRANTS</p>		\$ 787,500

FEDERAL CONSTRUCTION GRANTS

<p>NIH <i>Construction of Rhesus Macaque Facility</i> Dr. John VandeBerg, principal investigator</p>	2 years	\$ 2,000,000
<p>NIH <i>ABSL2 Chimpanzee Facility Improvement</i> Dr. John VandeBerg, principal investigator</p>	1 year	\$ 680,000
<p>NIH <i>Improvement of Animal Facility</i> Dr. John VandeBerg, principal investigator</p>	1 year	\$ 492,227
<p>TOTAL FEDERAL CONSTRUCTION GRANTS</p>		\$ 3,172,227



COMMERCIAL RESEARCH CONTRACTS
Major Research Contracts (\$100,000 or more)

	<i>Total Amount to SFBR</i>
Department of Comparative Medicine (7)	\$ 2,307,663
Department of Virology and Immunology (4)	\$ 735,276
Department of Physiology and Medicine (1)	\$ 134,304
Miscellaneous (under \$100,000 each)	\$ 1,714,272
TOTAL COMMERCIAL CONTRACTS	\$ 4,891,515
TOTAL OF NEW GRANTS AND CONTRACTS AWARDED IN 2002	\$45,880,224

Highlights of Scientific Progress in 2002

Major Grant Renewals for Research on Cancer Therapy, Reproductive Medicine, and the Genetics of Heart Disease in Mexican Americans

dr. P.N. Rao received a 5-year renewal of his contract with the National Institute for Child Health and Human Development to fund an organic synthesis facility to make new steroid hormones for cancer therapy and reproductive medicine. This represents over 20 years of consecutive funding of Dr. Rao's program by the National Institutes of Health (NIH).

Dr. Jean MacCluer was awarded a competitive grant renewal by the National Heart, Lung and Blood Institute for the San Antonio Family Heart Study. This ensures funding for years 15 through 20 of this, the most comprehensive study to date on the genetics of heart disease and its common correlates in Mexican Americans. The study is making marked progress in its efforts to identify genes that influence susceptibility to major complex metabolic diseases such as obesity, diabetes, atherosclerosis and hypertension. To date, scientists working with the project have localized more than 20 genes influencing such traits as cholesterol; insulin and glucose levels; leptin levels, which affect appetite; and an individual's fat mass.

Award-Winning Efforts in Statistical Genetics

Dr. John Blangero received a MERIT Award from the National Institutes of Health for his research program that is developing innovative statistical genetic methods. These methods are used by the Genetics Department as well as by investigators at other institutions throughout the international



scientific community to analyze genetic data obtained from large families in which diseases appear to be inherited. Highly prestigious, the MERIT Award is given to less than one percent of NIH awardees and will add an extra five years of support to Dr. Blangero's current grant for this research program, for a total award of 10 years.

Progressive New Research on Clotting Disorders

Dr. Laura Almasy received an NIH grant award to start a new research program investigating genetic factors that contribute to clotting disorders. This new



program has already identified three genetic locations associated with factors that produce thrombosis.

Novel Discovery About Parasitic Infections

The locations of two genes that contribute to susceptibility to roundworm infection were identified. This is the first evidence establishing that human host genes influence susceptibility to a parasitic infection. Since roundworm infection has always been thought to be simply a function of poor environmental quality, the identification of genetic influences on the disease represents a major change in the understanding of how intestinal worm infections develop.

Improved Methods for Understanding Malaria's Drug Resistance

The malaria research program in the Department of Genetics developed a new method for rapidly genotyping malaria parasites. This technique will facilitate research at SFBR and other institutions in identifying genetic mechanisms that contribute to the development of drug-resistant malaria parasites.

Promising Findings Related to Biodefense

In collaboration with scientists at The University of Texas at Austin, scientists in SFBR's Department of Virology and Immunology demonstrated that an antibody that recognizes anthrax toxin protects rats from exposure to the toxin. This will lead to a major new research program to further develop this approach for treating anthrax infection.

Identifying Possible New Methods to Treat HIV

Dr. Paul Zhou's program in HIV research developed methods for inducing HIV-infected cells to make intracellular antibodies to HIV. HIV replication in these cells was significantly attenuated, or weakened, suggesting that this novel method could be used to treat HIV infection. Dr. Zhou's program also developed new methods for introducing foreign genes into stem cells. This will be useful for developing a gene therapy treatment for HIV infection.

Breaking New Ground in the Fight Against Hepatitis C

The hepatitis C research program at SFBR has been the first to demonstrate that prior exposure to some strains of hepatitis C virus (HCV) protects chimpanzees against all strains of HCV. A follow-up of this study has suggested that it will be possible to design a vaccine that will provide protection against all forms of HCV infection.

scientific reports



Department of Genetics
Department of Virology and Immunology
Department of Physiology and Medicine
Department of Organic Chemistry
Department of Comparative Medicine
Southwest National Primate Research Center

S FBR's Department of Genetics works to advance human health through basic biomedical research with animal and human populations, specifically by characterizing the genetic components of susceptibility to common diseases of public health importance. Once the individual genes influencing a given disease are known, this genetic information can be used in drug development efforts to find more effective cures or methods of prevention for disease. The information can also be used to target available interventions to those individuals most likely to develop disease. During 2002, the scientists and staff of the Department of Genetics continued to make significant contributions to our understanding of the genetic determinants of a broad range of health problems, including cardiovascular, infectious and psychiatric diseases.

Cardiovascular Disease

Cardiovascular disease and its associated risk factors traditionally have been the primary focus of research in the Department of Genetics. Over 61 million Americans have cardiovascular disease, and almost 1 million people die of heart disease in the U.S. each year. Departmental research efforts in this area have included both human and animal studies.

For over 20 years, the pedigreed baboon colony at the Southwest Foundation has been used to assess the genetic determinants of response to dietary fat and cholesterol. Research on cardiovascular disease in humans has focused on assessing the genetic components of risk factors

for heart disease in minority populations, including Mexican Americans in San Antonio, Eskimos in Alaska, and Native American groups from Arizona, the Dakotas, and Oklahoma.

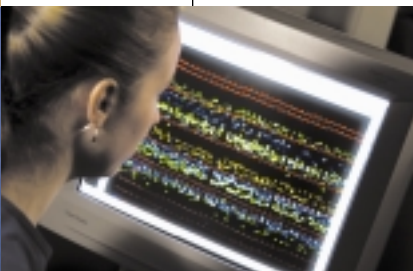
The general approach used by departmental



Sarah Williams-Blangero, Ph.D.
Chair

scientists to find genes influencing susceptibility to cardiovascular disease is to assess linkage between an unknown gene influencing a given disease-related trait and a large number of genetic markers evenly spaced across all the human chromosomes. When a genetic marker and a disease-related trait segregate together throughout a pedigree, the gene which causes variation in the trait is known to be located at or near the genetic marker on the chromosome. Knowing where a disease-related trait is in the genome is the first critical step towards identifying that gene.

During 2002, departmental scientists were successful in obtaining several major new grants to support research on heart disease. Dr. Jean MacCluer and her colleagues were awarded a program project grant from the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH) to continue their research on the genetics of heart disease in the Mexican American population through the San Antonio Family Heart Study. The



five-year, \$10.8 million grant will continue support for this important research program through its fifteenth year. Dr. Xing Li Wang received a \$1.8 million grant from the NHLBI to explore how infection with human cytomegalovirus may be involved in development of cardiovascular disease. Finally, Dr. Laura Almasy received a \$1.3 million grant from the NHLBI in support of her work on the genetic components to thrombosis, a blood-clotting disorder. This research program is being conducted in collaboration with investigators based at the Hospital St. Pau in Barcelona, Spain.

The research collaboration on thrombosis produced two major papers in 2002. The most common risk factor for thrombosis is activated C protein resistance (APCR). As reported in the scientific journal *Blood*, Drs. John Blangero, Laura Almasy, and colleagues localized a novel gene influencing APCR on chromosome 18. This gene also was determined to influence another important risk factor for thrombosis, Factor VII levels. In a paper published in the *American Journal of Human Genetics*, the same research group documented two genes influencing plasma levels of another significant risk factor for thrombosis, factor XII, including one not related to the Factor XII structural locus.

A number of important publications also resulted from the cardiovascular disease program this year. High density lipoprotein cholesterol (HDL-C), also known as “the good cholesterol,” is associated with diminished risk of heart disease in both humans and baboons. Dr. John Blangero was the senior author on a paper published in *Nature Genetics* by investigators associated with the San Antonio Family Heart Study. The paper reported the results of a linkage analysis which localized a gene on chromosome 9 that influences HDL-C concentrations in two populations of Mexican Americans. Another gene’s effects on HDL-C were documented in the journal *Arteriosclerosis, Thrombosis and Vascular Biology*, in a paper by Michael Mahaney and colleagues from the San Antonio Family Heart Study. These analyses of

data from Mexican American families indicated the important role of a gene located on chromosome 16 in determining plasma HDL-C levels.

In a separate effort, Dr. Laura Cox developed a highly novel approach for identifying genes localized by linkage analysis. This original strategy, published in *Genome Research*, utilizes a chromosomal region expression array to determine which genes have different levels of expression in the area known from the linkage analyses to contain the gene influencing a given trait. Scientists can then use this information to better determine which genes are worth pursuing further in gene identification efforts. This new approach promises to dramatically improve molecular genetic characterization and identification of genes linked to disease-related traits. Already, it is being used to narrow in on a gene influencing HDL cholesterol.



Infectious Disease

The department’s research program on the genetics of infectious diseases started seven years ago with a single grant. It is now the second most highly funded area of research in the department. This program involves research at several international field sites, including a project based in Thailand on the genetic determinants of drug resistance in malaria parasites, research based in Brazil on the genetic components of susceptibility to Chagas disease, and a project based in Nepal on the genetics of susceptibility to intestinal worm infections. The Jiri Helminth Project in Nepal received additional support this year with a subcontract totaling \$541,956 funded by the National Institute of Child Health and

Development to support an assessment of the impact of helminthic infection on growth and development in the Jirel population.

The research on intestinal worm infections in Nepal produced a major result this year with the localization of two genes influencing susceptibility to infection with roundworm (*Ascaris lumbricoides*). A paper published in the *Proceedings of the National Academy of Sciences* by Dr. Sarah Williams-Blangero and colleagues presented the first localization of genes that influence susceptibility to intestinal helminths, a class of diseases which affects a quarter of the world's population. Efforts are now underway to identify the specific genes involved.

Animal Model Development

Animal model development has been a major area of research in the department throughout its history. Scientists in the Department of Genetics pioneered the development of the laboratory opossum as an animal model for a broad range of research programs. This animal, *Monodelphis domestica*, is now the most widely used marsupial in biomedical research. During 2002, Dr. Brad Wang received a \$20,000 grant from the San Antonio Area

Foundation to expand the use of this unique animal model to research on mechanisms of repair in spinal cord injuries. The *Monodelphis* colony resource was supported by a generous grant from the Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation, which has supported the colony throughout its history.

Over the last 20 years, scientists in the Genetics Department have also been heavily involved in the refinement of the baboon as an animal model in biomedical research, particularly in the area of cardiovascular disease. The pedigreed baboon colony has become a major national resource for research on the genetic components of heart disease, osteoporosis, Chagas disease, and aging. This year, Dr. Jeff Rogers received a \$1.2 million five-year grant award from the National Center for Research Resources of the NIH to support the continued genetic characterization of the baboon model in addition to refining genetic information available for another commonly used primate model, the rhesus macaque.

Statistical Methods Development

The development of new statistical methods for genetic epidemiological research, and in particular for linkage analysis, has been a long-term and highly successful focus of research in the department. Departmental scientists were the first to perform statistical genetic analyses in parallel using a computer cluster, partitioning complex analyses among different computers in order to increase the speed with which those analyses could be completed. This year, Dr. Bennett Dyke received a \$228,000 grant from the National Center for Research Resources at NIH to continue expansion of the computer cluster. Over the past four years, a tremendous increase in capabilities has been achieved. Analyses that took two weeks to complete in 1998 can now be completed in two days. When the planned expansion of the cluster is completed in 2003, analyses which now require 48 hours will take just three minutes. The expanded cluster will be housed in the new SBC Genomics



Computing Center, which has recently been completed. This new center will enable departmental scientists to pursue the hunt for genes influencing common diseases at an unprecedented pace.

Psychiatric Disease

Research on the genetic determinants of psychiatric disease and its correlates is one of the newest programs in the department. To date, research efforts in this area have focused mainly on human populations. However, an exciting new grant awarded to Dr. Jeff Rogers this year will expand the program to the use of the baboon model. Dr. Rogers received a \$1.9 million award from the National Institute for Mental Health of the NIH to support assessment of the genetic determinants of physiological traits known to be associated with risk for depression and other mental illnesses in the pedigreed baboon population.

Diabetes

For the last 10 years, the Department of Genetics has maintained a small research program in diabetes. This disease is a major public health problem, particularly in the Mexican American population, and has been the focus of research on cardiovascular disease by departmental scientists. In 2002, the diabetes research program was greatly strengthened with the recruitment of Dr. Ravindranath Duggirala. Dr. Duggirala brought three NIH grants with him to support his research on the genetic components of susceptibility to diabetes and related disorders. This new research effort promises to become a major program in the department.

Already, Dr. Duggirala has made significant process in understanding the genetic determinants of the insulin resistance syndrome that is associated with diabetes. Insulin resistance is associated with obesity, hypertension, cholesterol levels, and a variety of other traits related to diabetes. Analyzing a range of traits that characterize insulin resistance syndrome, Dr.



Duggirala found strong evidence for the roles of genes on chromosomes 6 and 7 in determining the insulin resistance syndrome in nondiabetic Mexican Americans.

Aging

One of the newest research areas developing in the department concerns the genetics of aging. Although this program does not yet have any dedicated funding, research on age-related traits is being conducted in association with other projects as a way of developing a base upon which future research efforts specifically focused on aging can be built. As is the case in many of the Department's programs, research efforts focused on aging have included studies of both humans and the baboon model. Dr. Ravi Duggirala published a paper in Genetic Epidemiology that documented significant genetic effects on markers of biological age in a Mennonite population. Between 27 and 47 percent of the variation in measures of biological aging was attributable to genetic factors. Drs. Lisa Martin and Tony Comuzzie considered the genetic determinants of lifespan in the pedigreed baboon population and determined that approximately 23 percent of the variation in lifespan was due to genetic effects.

Summary

The year 2002 was a year of great achievements for the Department of Genetics, with scientists generating a record-level of grant income for the year. Departmental scientists produced 64 contributions to the scientific literature, including nine which reported the localization of new genes responsible for differential susceptibility to heart disease, thrombosis, psychiatric disease, and parasitic disease. Through development and refinement of research techniques, they also expanded the arsenal of statistical and molecular genetic tools available to facilitate future

research efforts on a broad range of diseases.

While the department experienced its greatest success ever in obtaining NIH funding for genetic research, it is also important to note that philanthropy has never been more important to this department's achievements. As the department continues its rapid growth, it is impossible to rely solely on funding from the National Institutes of

Health. The donations that the Foundation has received in support of the endowment, pilot projects, the SBC Genomics Computing Center, the animal resources, and faculty recruitment have all been critical to the success of the department. The scientists and staff of the Department of Genetics are grateful to the Foundation's administration, the Board of Trustees, and the many individuals, private foundations and funding agencies listed in this report for their continuing support of genetic research at SFBR.



Doctoral Staff

(as of December 2002)

Chair

Sarah Williams-Blangero, Ph.D.

Scientists

John Blangero, Ph.D.

Bennett Dyke, Ph.D.

Jean W. MacCluer, Ph.D.

Michael C. Mahaney, Ph.D.

David L. Rainwater, Ph.D.

Jeffrey A. Rogers, Ph.D.

John L. VandeBerg, Ph.D.

Director, Southwest National Primate Research Center

Associate Scientists

Laura A. Almasy, Ph.D.

Anthony G. Comuzzie, Ph.D.

Ravindranath Duggirala, Ph.D.

Paul B. Samollow, Ph.D.

Xing Li Wang, M.B.B.S., Ph.D.

Assistant Scientists

Timothy J.C. Anderson, Ph.D.

Jeff T. Williams, Ph.D.

Staff Scientists

Gerome Brush II, Ph.D.

Jeannie Chan, Ph.D.

Shelley A. Cole, Ph.D.

Laura A. Cox, Ph.D.

Sandra L. Laston, Ph.D.

Dev R. Rai, M.D.

Ying H. Shen, Ph.D.

Jian Wang, M.D., Ph.D.

Zhiqiang Wang, Ph.D.

Postdoctoral Scientists

Harald H.H. Göring, Ph.D.

Nicholas Gouin, Ph.D.

Lorena M. Havill, Ph.D.

Lisa Martin, Ph.D.

Muthuswamy Raveendran, Ph.D.

Cherise J. Rohr, Ph.D.

Xing-Jun Shen, Ph.D.

Qiang Shi, Ph.D.

Alloysius J. Budi Utama, Ph.D.

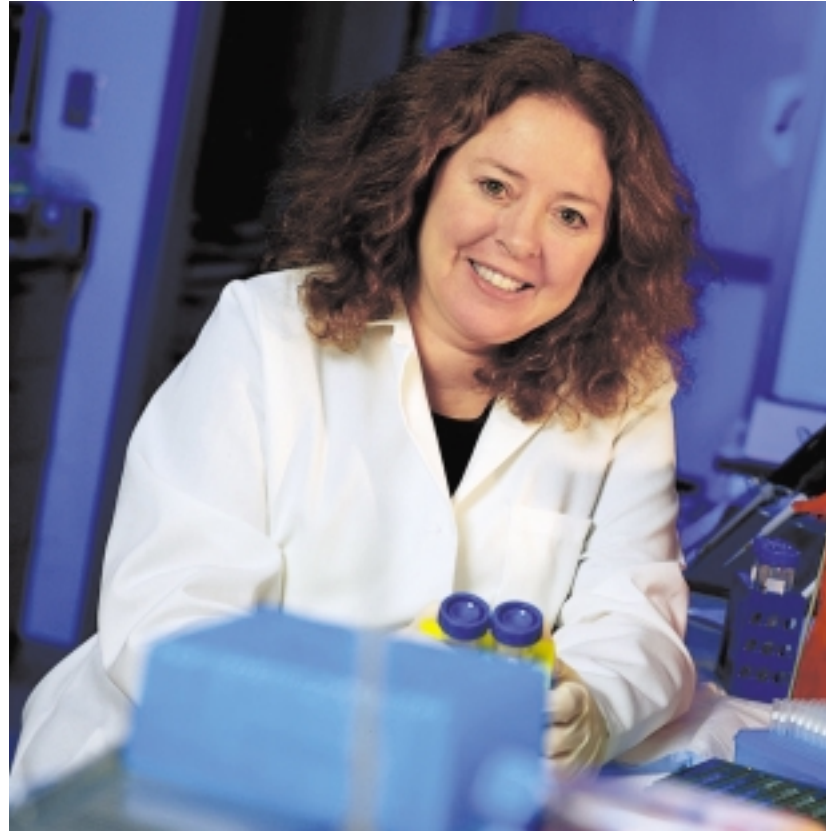
to defeat viruses that cause AIDS, hepatitis, herpes, hemorrhagic fevers, and a host of other maladies that plague our world, scientists in the Department of Virology and Immunology try to attack viruses on two different fronts. First, they examine how viruses replicate and propagate so as to identify their Achilles' heel. Second, they study how the immune system recognizes a virus and how best to stimulate immune response to clear viral infections. With this knowledge, scientists hope to develop new drug therapies to treat viral infections, as well as vaccines to prevent those infections in the first place.

Giving SFBR virologists advantages in their life-saving quest are two of the Foundation's unique resources. The department's state-of-the-art facilities include the nation's only privately owned biosafety level four (BSL-4) maximum containment laboratory. This facility – which has proven especially beneficial in support of the nation's biodefense efforts – allows Foundation scientists to safely study lethal pathogens for which there currently is no known treatment or cure.

Also extremely valuable are the nonhuman primates housed at the Foundation. 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.

Emerging and Exotic Viruses

Dr. Jean Patterson continues to study the pathogenesis of Leishmaniavirus, which is associated with lesions of the skin (cutaneous form) and the mucous membranes of the mouth (mucocutaneous form). Because military personnel are at risk of contracting the disease when deployed to various regions of the world, the Department of Defense has sought assistance in understanding how the infection develops and in the development of tests that allow rapid diagnosis of the disease. As part of her efforts in this area in 2002, Dr. Patterson completed the



Jean L. Patterson, Ph.D.
Chair

characterization of all enzymes and nucleic acids of the life cycle of this virus.

Dr. Patterson also began work on the development of a vaccine for Lassa fever virus. An arenavirus that causes hemorrhagic fever, Lassa fever affects between 300,000 and 500,000 people in West Africa. In collaboration with the Institute of Human Virology at the University of Maryland, Dr. Patterson and her team have begun tests on a live attenuated vaccine.

Dr. Alex Hamill in her group recently developed a high-throughput antiviral screen specifically for viruses that can only be studied in BSL-4 laboratories. Currently, he is testing natural products from Uganda

as potential drugs against Ebola virus and Lassa fever.

Through other research efforts, Dr. Patterson and her team continue to work with the Department of Defense on projects involved with government's attempt to block the proliferation of biological weapons, including anthrax, tularensis, and other select agents.

In Dr. Rebeca Rico-Hesse's laboratory, the research focus is on dengue and other emerging viruses that exist in neighboring countries and threaten to become prevalent in the United States. In 2002, she and her research team studied the basic biology of viruses of two different families that cause hemorrhagic fevers in tropical and sub-tropical areas of the world, including the southern United States. For dengue viruses, which are transmitted by mosquitoes, her laboratory's long-term goals are to determine the structural (RNA and/or protein) and transmission (replication in *Aedes aegypti*) characteristics of dengue type 2 virus variants that have produced dengue hemorrhagic fever in humans throughout the world. Dr. Rico-Hesse and her research team also are studying South American arenaviruses that cause hemorrhagic fever, and they recently determined the primary structure of the viral RNA of those described to date in the American continent. Most of these viruses are transmitted to humans by rodents, and Dr. Rico-Hesse's team is attempting to identify the viral structures that cause human disease. The identification of viral structures associated with virulence will help in the identification of vaccine targets.

Hepatitis

The prevalence of chronic hepatitis C virus (HCV) infection is estimated at 3 percent worldwide and at more than 2 percent in the United States. This increases to 4 percent for people between the ages of 40 and 60, and to more than 30 percent for people with AIDS. Although a person with HCV infection can remain asymptomatic for decades, approximately

20 percent of infected individuals will eventually develop significant liver disease, including cirrhosis and liver cancer. The leading cause of liver failure and liver transplantation, HCV infection also accounts for approximately 25 percent of all hepatocellular carcinomas. Consequently, there is significant interest in vaccine development.

Since acute HCV infection is uncommonly recognized in humans, much of the scientific understanding of viral recovery derives from studies in chimpanzees, the only animal besides man that is vulnerable to HCV infection. Early seminal work was discouraging, indicating that chimpanzees who recovered from HCV infection could be reinfected with the same inoculum. However, recent findings by SFBR's Dr. Robert Lanford are much more encouraging, demonstrating protective immunity following rechallenge. Because different genotypes of HCV display extraordinary genetic and antigenic diversity, it was at first unclear whether the protective immunity Dr. Lanford's team demonstrated against a genotype 1 infection would be sufficiently broad to



confer protection across the four HCV genotypes. But in 2002, the group demonstrated the first evidence that prior infection with genotype 1 provides protective immunity to other HCV genotypes, even when animals are challenged with a highly complex mixture containing four genotypes. These studies, then, are the first to demonstrate the feasibility of developing a vaccine protective against all HCV strains.



Retroviruses and AIDS

Despite progress made in the fight against AIDS, the World Health Organization still estimates that this devastating disease will take the lives of nearly 68 million people over the next 20 years. That is why SFBR researchers continue

to follow a number of different approaches in their efforts to combat this worldwide epidemic.

Dr. Jonathan Allan is working to understand how HIV induces AIDS in people by studying simian immunodeficiency viruses (SIV) in their natural host, with particular attention paid to the discovery of how seemingly harmless viral infections in monkeys can pose a serious health risk to humans. Therefore, his laboratory has developed several nonhuman primate models for research on human diseases including not only AIDS but also cancer. Dr. Allan recently developed a core retroviral diagnostic laboratory under the auspices of the Southwest National Primate Research Center and is presently providing expertise and screening for simian retroviruses that could potentially infect humans.

Dr. Luis Giavedoni, who also studies simian immunodeficiency viruses, recently initiated the first phase of a study to determine the role of regulatory

receptors on CD8+ cells during SIV infection. CD8+ cells encompass both cytotoxic T cells (CTLs) and natural killer cells (NK cells), which are essential components of the immune system for the control of viral infections.

The main focus of Dr. Krishna Murthy's research is pathogenesis of viral infections, immune response of the host to infections, and candidate vaccine strategies. A majority of his studies are being performed using human and nonhuman primate samples from hosts exposed to human immunodeficiency viruses and various hepatitis viruses.

Dr. Murthy works with the National Institutes of Health and several commercial ventures in testing vaccines to prevent HIV infection. Ongoing AIDS vaccine studies include determining the safety and efficacy of recombinant gp120 subunit, as well as DNA vaccines in the chimpanzee model. One of the gp120 vaccines tested is undergoing final Phase III trials in 12,000 human volunteers in the United States, Canada and Thailand. Because of the central role played by T cells in general, and CD8+ T cells in particular, their function in vaccinated animals is being evaluated.

Dr. Murthy's laboratory also provides basic clinical immunology support for both intramural and extramural investigators utilizing nonhuman primate models. This support includes the analysis of many molecules involved in the immune system.

Research in Dr. Paul Zhou's laboratory mainly focuses on developing immune-based strategies against HIV infection. In



2002, his program developed methods for inducing HIV-infected cells to make intracellular antibodies to HIV. HIV replication in these cells was significantly attenuated, or weakened, suggesting that this novel method could be used to treat HIV infection. Dr. Zhou's program also developed new methods for introducing foreign genes into stem cells. This will be useful for developing a gene therapy treatment for HIV infection.

The major effort in Dr. Jason Kimata's lab is to use the SIV macaque model to answer questions about HIV transmission and pathogenesis. Previously, Dr. Kimata cloned several SIV mutants from different stages of infection and disease and demonstrated that variant viruses that emerge during the course of infection drive progression to AIDS. A second area of interest has been the development of the SIV macaque model to investigate whether a lectin binding protein (DC-SIGN) – which is predominantly expressed on dendritic cells (DCs) and can capture HIV – plays a critical role in HIV or SIV infection and replication in the host.

Herpes Simplex Virus

An important cause of sexually transmitted disease, herpes simplex virus (HSV) also causes significant disease in neonates and immunocompromised individuals and is the leading cause of blindness due to infection in the United States.

Dr. David Martin's efforts to combat the disease are focused on herpesvirus biology and include both applied and basic research. In addition to his efforts to develop better systems for studying the biology of the virus, he also is investigating the use of HSV as a delivery system for vaccines against various diseases. This delivery system is an attractive vaccine candidate because it can package a large number of genes and is able to enter a wide variety of cell types.

A collaborative project with investigators from the Department of Genetics also seeks to define the role of herpesviruses in the development of atherosclerosis.

Doctoral Staff

(as of December 2002)

Chairman

Jean L. Patterson, Ph.D.

Scientists

Jonathan S. Allan, D.V.M.

Robert E. Lanford, Ph.D.

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

Rebeca Rico-Hesse, Ph.D.

Associate Scientists

Luis D. Giavedoni, Ph.D.

Paul Zhou, Ph.D.

Assistant Scientists

Jason T. Kimata, Ph.D.

David W. Martin, Ph.D.

Staff Scientists

Catherine B. Bigger, Ph.D.

F. Alex Hamill, Ph.D.

Vida L. Hodara, Ph.D.

Postdoctoral Scientists

Philip Armstrong, Sc.D.

John E. Bigger, Ph.D.

Raymond G. Cologna, Ph.D.

S. Denise Goens, Ph.D.

Seung Jae Lee, Ph.D.

Lisa Lott, Ph.D.

Previous studies have shown that infection of cells that line the blood vessels with the herpesvirus cytomegalovirus (CMV) may serve as a catalyst for the development of plaques that can restrict blood flow to the heart. Dr. Martin has initiated a series of studies that will determine if HSV plays a similar role in atherosclerosis, with the expectation that his research findings will identify new targets and pathways for therapeutic intervention into the process of this major contributor to heart disease.

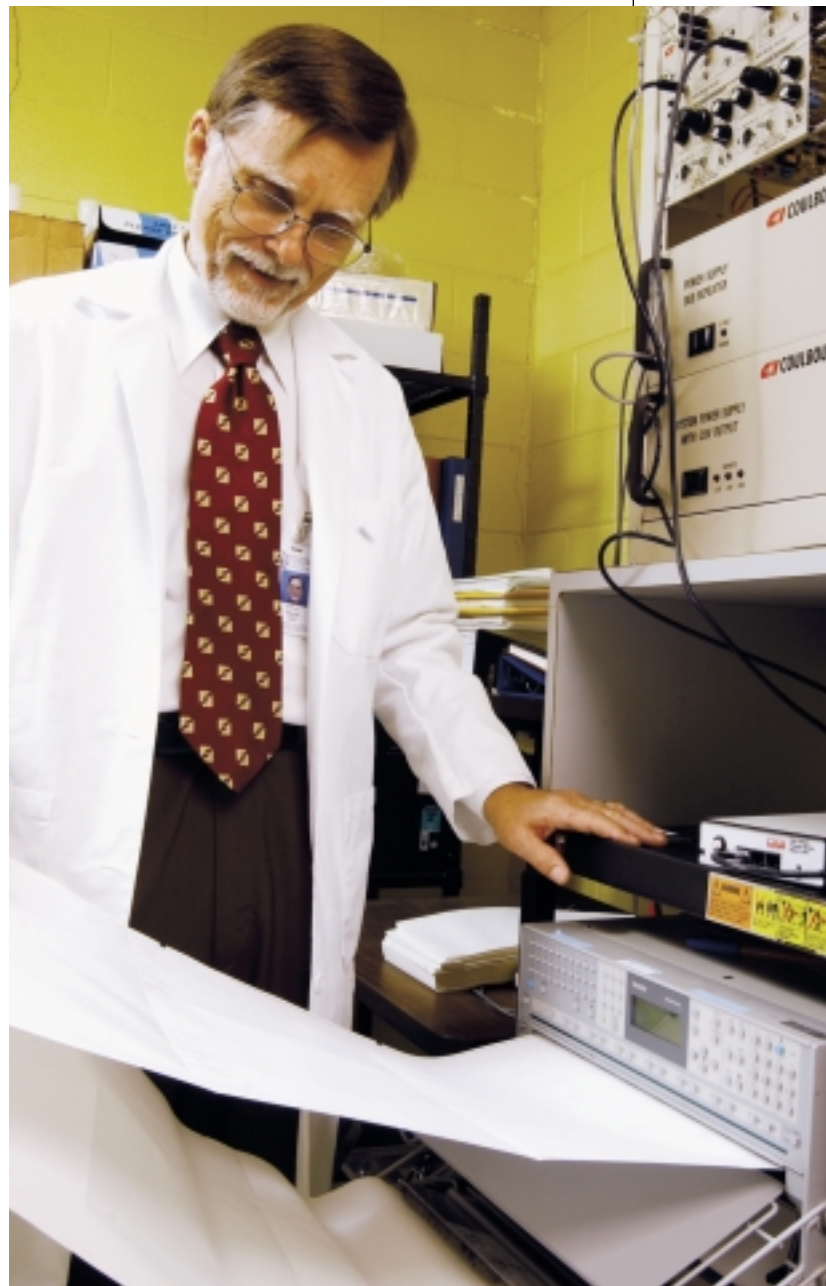
Research in the Department of Physiology and Medicine focuses on two major areas of biomedical research, cardiovascular diseases and cancer drug discovery. The following is a summary of the significant research findings in the department reported during 2002. A feature common to all of these programs is the extensive collaborative nature of the research, which includes investigators at many institutions throughout the United States and around the world.

Evidence that Fat Puts Young People at Risk for Adult Coronary Heart Disease

One of the department's collaborative studies – which brings together investigators from SFBR, the University of Texas Health Science Center at San Antonio, Ohio State University, and the Louisiana State University Health Science Center – has produced startling evidence about how coronary heart disease (CHD) begins to develop in young persons.

Over a seven-year period, investigators with the Pathobiological Determinants of Atherosclerosis in Youth Study collected autopsy specimens and information from adolescents and young adults aged 15-34 who had died of external causes, such as a car accidents. This information, gathered from 2,133 men and 688 women, has since been used by the researchers to examine the relationship between the risk factors for adult CHD and the early stages of atherosclerosis in the young people's coronary arteries. The tissue changes of atherosclerosis are responsible for obstruction of the coronary arteries and heart disease in middle age and later.

Alarmingly, scientists found that, even in these young people, the well-known risk factors for adult CHD (blood cholesterol, hypertension, smoking, diabetes) are associated with more rapid progression of coronary atherosclerosis. A recent analysis of these data, published in a paper authored by Dr. Henry McGill at SFBR and his collaborators, focused on the effects of obesity and body fat distribution.



Robert E. Shade, Ph.D.
Scientific Director and Acting Chair

In adolescent and young adult males, obesity was associated with both the size of atherosclerotic plaques and with characteristics that made them more susceptible to rupture and thrombosis, the events that lead directly to heart attacks. In females, obesity was only weakly associated with coronary atherosclerosis, probably because atherosclerosis develops about 10 years later in women than in men. Abdominal fat was even more strongly associated with advanced coronary atherosclerosis than overall body fat.

Because it shows how excess body fat can negatively affect human health even at a young age, this study has been cited by the American Heart Association as further evidence of the need for increased public health efforts to reverse the recently identified epidemic of childhood obesity in the United States.

The Impact of Stress on Salt Intake and Cardiovascular Disease

While body fat is a contributor to heart disease, dietary salt intake also is known to be a major risk factor for cardiovascular diseases such as hypertension, atherosclerosis, and stroke. However, there are no known therapeutic approaches that will reduce one's inclination to consume salt, or salt appetite.

In SFBR's Department of Physiology and Medicine, Dr. Robert Shade leads a research program trying to find ways to help curb humans' appetite for salt by defining the neural mechanisms that promote salt appetite in baboons. Because baboons are so similar to humans in their genetics and physiology, it is believed that what investigators learn from this nonhuman primate will have direct application to human health.

In this research effort, scientists at SFBR are collaborating with investigators at the Howard Florey Institute for Experimental Physiology and Medicine in Melbourne, Australia, and the Clayton Foundation

Laboratories for Peptide Biology at the Salk Institute.

The Australian group's previous research with other species such as sheep, rabbits and mice showed that hormones involved in stimulating the adrenal gland's response to stress caused these animals to dramatically increase their salt intake. These studies thereby suggested that stress might contribute to salt appetite. However, the same response did not hold true in similar studies with baboons, in which stress hormones associated with the adrenal system showed no effect on salt ingestion.

While this portion of the hormonal response to stress may not increase salt appetite in primates, including humans, stress hormones still appear to play a

key role. In fact, subsequent research at SFBR has revealed that another hormonal system that also increases with stress, the renin-angiotensin-aldosterone system, may be the primary regulator of salt appetite in baboons. Research results published in 2002 demonstrated that increased levels of aldosterone and angiotensin intensify salt appetite. This is in addition to the hormones' already known effect of causing salt retention. A major implication of this finding is that, since both angiotensin and aldosterone are increased with congestive heart failure, salt appetite may be increased in a disease situation that requires salt intake to be as low as possible. On the positive side, it also suggests that blocking these hormones in patients with congestive heart failure could be therapeutic.



**Cancer Drug Discovery Program
 Examines Marine Life**

The cancer drug discovery program headed by Dr. Susan Mooberry in the Department of Physiology and Medicine studies numerous types of plant and marine life in the search for natural compounds to provide new, less toxic ways to fight cancer. Among its accomplishments in 2002, this program published a promising finding involving a food source of the sea hare.

Dr. Mooberry's lab collaborated with investigators at the University of Hawaii, the University of Guam Marine Laboratory, and the Karmanos Cancer Center at Wayne State University to report the discovery of a new compound, symplostatin 3, that has activity against human cancer cell lines.

This compound is similar to another compound, dolastatin, which is currently in human clinical trials as a chemotherapy agent for the treatment of cancer.

Dolastatin was originally isolated from a marine invertebrate, the sea hare, an opisthobranch mollusk.

Collaborative studies involving SFBR scientists tested the hypothesis that dolastatin-like compounds or analogues are present in sea hares only because these compounds are actually synthesized by cyanobacteria, which are a major food source for the sea hares. Investigators isolated several dolastatin-like compounds from



Doctoral Staff

(as of December 2002)

Acting Chairman

Robert E. Shade, Ph.D.
Scientific Director

Senior Scientist Emeritus

Henry C. McGill, Jr., M.D.

Scientists

Rampratap S. Kushwaha, Ph.D.
 Suzette D. Tardif, Ph.D.
*Associate Director, Southwest National
 Primate Research Center*

Associate Scientist

Susan Mooberry, Ph.D.

Postdoctoral Scientist

Tina L. Tinley, Ph.D.

cyanobacteria, and one of these new compounds was given the name symplostatin 3.

Studies conducted at Southwest Foundation demonstrated that symplostatin 3 disrupts cellular microtubules in cancer cell lines. This is an important property in potential new cancer therapy drugs because microtubules are cellular structures that guide genetic material into the two daughter cells during cell division. The disruption of their normal function inhibits cell division and signals cancer cells to initiate their own death, essentially turning on a cellular suicide program.

While Dr. Mooberry's research has yielded promising findings related to symplostatin 3, it also provides support for searching for additional new anticancer compounds that are synthesized by cyanobacteria.

in April 2002, the Department of Organic Chemistry initiated year one of a new 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. The year 2002 marked the 28th consecutive year that the department has served in this capacity through a number of contracts.

These contracts were awarded on a competitive basis, and the Department of Organic Chemistry has been consistently recognized as the premier research group in the nation for steroid synthesis. Over the years, the department has 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 programs are based upon sophisticated synthetic organic chemistry and are directed toward the construction of molecular structures of natural or designed origins. Emphasis is placed on biomedical relevance and the development of novel and efficient synthetic techniques. Current projects and areas of interest include:

Antiprogestins

The hormone progesterone plays a crucial role in female reproduction. Some of the important reproductive events include: (1) regulation of cellular function via control of protein synthesis, (2) induction of ovulation, (3) regulation of tubal transport of fertilized ova, (4) transformation of the endometrium for implantation, and (5) maintenance of pregnancy. Agents that interfere with or block the binding of progesterone to its receptor are known as antiprogestins or selective progesterone receptor modulators (SPRM).

The discovery of synthetic antiprogestational agents represents a significant milestone in



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

reproductive endocrinology. These compounds have been shown useful for cervical ripening, thus facilitating labor, and as a highly effective postcoital therapy for emergency contraception. The potential applications of antiprogestins involve contraception as well as treatment of conditions where the presence of progesterone is contradicted. Such conditions include endometriosis, progesterone dependent tumors, uterine fibroids, premenstrual syndrome, and adverse symptoms of menopause.

The antiprogestin known as CDB-4124 was conceived and synthesized in our laboratories. Subsequent biological testing indicated this analog exhibited three times the antiprogestational activity of the parent compound with significantly decreased side effects. This compound has been licensed to

Zonagen Inc. for development in the treatment of endometriosis. Preliminary primate studies indicate that CDB-4124 can significantly reduce endometrial lesions without altering bone density or lowering glucocorticoid levels.

Subsequent to the synthesis and biological testing of CDB-4124, the department focused its efforts on the development of a practical method for the synthesis of large quantities of this material. Using the procedures developed their laboratories, SFBR chemists are currently synthesizing a large quantity of CDB-4124 under “good manufacturing practices” for preclinical studies including toxicology and genotoxicity studies in animal models. The methods developed here for the synthesis of CDB-4124 are the subject of a pending world patent.

Male Contraceptives

While most of the work in contraceptive development has been aimed at the regulation of female fertility, recent years have seen efforts at the regulation of male fertility. Effective regulation of male fertility requires lowering sperm count, which can be done through the administration of gonadotropin releasing hormone (GnRH) antagonists. These compounds cause the depletion of testosterone in the testes, leading to cessation of sperm production.

However, decreased levels of testosterone leads to a loss of libido and other undesirable side effects. To counter these, it is necessary to administer supplemental testosterone derivatives. In most instances, this requires daily injections of testosterone analogs. This regime is considered unacceptable as a means of regulating male fertility.

A more 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 $7\alpha,11\beta$ -dimethyl-19-nortestosterone (Dimethandrolone) has approximately three times the activity of testosterone and a longer duration of action.

The reported synthesis of Dimethandrolone is rather lengthy (13 steps) and involves the formation of intermediates that have been demonstrated to be unstable. Consequently, Dr. Pemmaraju N. Rao and his research team have developed a shorter (8 step), more efficient synthesis of this material that avoids unstable intermediates and is adaptable to large-scale synthesis under “good manufacturing practices” (GMP) conditions. They currently are synthesizing a large quantity of Dimethandrolone under “good manufacturing practices” for preclinical studies. The methods they have developed for the synthesis of this material are the subject of a pending world patent.

Novel 2-Methoxyestradiol Compounds with Activity Against Cancer Cells and Tumors

Estradiol is the primary mammalian sex hormone responsible for development of most of the female secondary sexual characteristics. During puberty, estradiol causes proliferation and growth of hormone-sensitive tissue such as the breast and uterine lining. Estradiol also causes a proliferation of the endometrial cells in preparation for pregnancy. The sequential biochemical hydroxylation and methylation of estradiol gives rise to the natural metabolite 2-methoxyestradiol (2-ME2). 2-Methoxyestradiol is a natural metabolite of estradiol devoid of estrogenic or tumor promoting activity *in vivo*.

Back in the 1960s, Dr. Rao was one of the first scientists to synthesize 2-ME2 and in subsequent years developed numerous derivatives as potential cholesterol lowering agents. Although these efforts met with limited success, research in this area was refocused towards non-steroidal analogs due to



concerns about potential estrogenic (feminizing) side effects.

Interest in 2-methoxyestradiol was rekindled in 1989 upon discovery 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. Initiation of either of these events will cause tumors to shrink, but the combination of effects may provide significant advantages over current anticancer therapies. The mechanism of action of 2-ME2 is disruption of cellular microtubules leading to cessation of cell division and initiation of programmed cell death.

Preclinical studies with 2-ME2 reveal that it is orally active, inexpensive to produce and, in contrast to most antitumor agents, exhibits no overall toxicity at therapeutically effective doses. Phase I clinical trials were initiated in the spring of 2000 to determine if 2-ME2 was safe for use in humans. The results suggest that 2-ME2 is safe, no life-threatening toxicities occurred during the trial and no maximal tolerated dose was achieved. Another trial was initiated in September of last year to evaluate the safety of combining 2-ME2 with a cytotoxic chemotherapeutic agent, Taxotere™ (a Taxol™ derivative). Phase II clinical trials were recently approved by the FDA to determine if 2-ME2 is effective against prostate cancer and human myeloma, a cancer resistant to most forms of therapy. The biological activities of 2-ME2 are generating considerable excitement because of its efficacy without toxicity. Because 2-ME2 is a promising drug for cancer therapy, work has begun on second-generation derivatives with superior properties, including better oral availability and different chemosensitivity profiles.

Upon learning these findings, the Department of

Doctoral Staff

(as of December 2002)

Senior Scientist and Chairman

Pemmaraju N. Rao, Ph.D.

Organic Chemistry initiated a program to investigate the potential anticancer application of prior and newly synthesized 2-ME2 derivatives. Based upon published results of several investigators, fifteen novel derivatives of 2-ME2 were designed and synthesized for testing. In collaboration with Dr. Susan Mooberry of the Department of Physiology and Medicine, these compounds tested for antiproliferative activity against breast and ovarian cancer cells. Three of the analogs were found to have promising activity. All three analogs disrupt interphase and mitotic microtubules, consistent with the mechanism of action of 2-ME2.

In subsequent biological tests, 14-dehydro-2ME2 was shown to be 15 times more potent than 2-ME2 for killing specific types of cancer cells and demonstrated an advantage against breast cancer in the mouse model. Another analog, 15-dehydro-2ME2, totally killed off prostate cancer cell lines, a result not seen with the parent 2-ME2 or any other analog. The third promising analog, 2ME2-15a,16a-acetonide, showed good antitumor activity in a mouse model for breast cancer. All of these promising results occurred at doses nontoxic to normal cells.

In December 2002, the results of some of these investigations were published in two articles in the journal *Steroids*. More detailed biological results were published in the April 2003 edition of *Cancer Research*. The methods developed at SFBR for the synthesis of these analogs and their biological effects are the subject of a pending world patent.

At the end of 2002 and beginning of 2003, the SFBR Department of Laboratory Animal Medicine underwent some significant changes, bidding farewell to its long-time chairman, welcoming a new chair, and garnering a new name, the Department of Comparative Medicine.

Saying Goodbye to a Distinguished Chair

After 18 years of dedicated and distinguished service to the department, including 16 years as chair, Dr. Thomas Butler officially retired in December. Always focused on the department's mission of providing the highest quality of care to SFBR's animal colonies and valuable research support to scientists, Dr. Butler also oversaw the department's tremendous growth during his tenure. As the Foundation, its research programs, its contracts with biotech organizations and the number of its animals grew, so did the department. With a staff of just 17 in 1984, today the department employs more than 100 personnel and maintains more than 6,000 nonhuman primates and 3,000 other animals in 254,210 square feet of facilities and two six-acre corrals to support more than \$14 million in biomedical research.

New Chair Brings New Vision as Department Sees Name Change

Now Dr. K. Dee Carey, who himself leads a distinguished career, has taken the reins as chair and is working diligently to move the department ahead even further. Dr. Carey has been with the Foundation since 1976, serving for the past two years as Acting Chair of the Department of Physiology and Medicine. His interest has been the development of animal models of human disease and the development of medical procedures to support unique research projects.

Assisting Dr. Carey in his leadership efforts is Dr. Larry B. Cummins, Associate Department Chair and



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

Director of Animal Resources. Dr. Cummins' background is in the use of great apes in biomedical research. In addition to providing that expertise to the department, he also helps oversee the design and construction of new animal facilities.

Under the direction of Drs. Carey and Cummins, Laboratory Animal Medicine has now become the Department of Comparative Medicine. As in the past, the department is still responsible for the daily maintenance, health care, and research support of several colonies of nonhuman primates and other animals. It also ensures that SFBR programs and facilities are in compliance with all state and national

accrediting body regulations and guidelines as they relate to research animal care and use. The Foundation has been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) since 1973.

However, the department's new name better reflects its important collaborative role with SFBR scientists and external investigators in conducting innovative scientific research.

In addition to the name change, the department also has gained some new faculty, as several veterinarians and scientists who used to work in Physiology and Medicine but relied heavily on this department's resources have now joined the faculty serving in Comparative Medicine. This move is intended to provide the two groups with central direction and allow their specialties and technical expertise and skills to be shared more effectively.

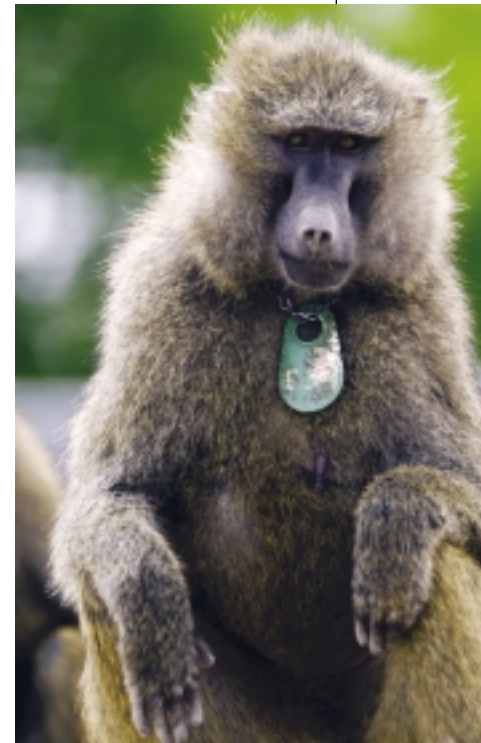
Current Activities and Progress

The Department of Comparative Medicine consists of three divisions: Animal Resources, Medicine, and Research Resources. Animal Resources is responsible for the daily maintenance of more than 6,000 nonhuman primates and 3,000 other animals as well as facilities maintenance, new facilities design, and oversight of facilities construction. The Medical Division includes veterinarians who support clinical and research activities, a veterinary pathology section that provides complete anatomic and clinical diagnostic capabilities, and staff who provide environmental enrichment. Research Resources includes sections that provide research coordination and project management, technical services that support clinical care and research projects, and the only intensive care unit dedicated to the baboon model of human premature lung disease.

Dr. Gene Hubbard directs the pathology section of the department. His interest is in describing and documenting in the literature infectious and naturally occurring disease processes in the nonhuman primate

colonies at the Foundation. He is recognized for his expertise in the pathology of age-related changes in rodents and nonhuman primates. Dr. Kathleen Brasky directs most of the research projects utilizing chimpanzees and has recently become the lead veterinarian for biomedical projects performed in the Foundation's biosafety level four (BSL-4) facility. Dr. Michelle Leland is a skilled surgeon who performs most of the clinical and experimental surgeries at SFBR, directs clinical care for the baboon hospital and the baboon infant nursery, and collaborates with scientists using the pedigreed baboon and rhesus colonies. Dr. Pat Frost is the principal investigator of an NIH grant to produce rhesus monkeys that are free of specific pathogenic viruses and are especially valuable models for AIDS research. She provides clinical care for the chimpanzee and cynomolgus colonies and research support for scientists using baboons and chimpanzees. Dr. Linda Brent developed and expanded the animal environmental enrichment program at the Foundation. Reviewers of the animal facility have acknowledged the program for its excellence.

The Department of Comparative Medicine maintains a variety of species including chimpanzees, baboons, African green monkeys, tamarins, spider monkeys, several species of macaque monkeys, rats, mice, rabbits, South American opossums, and guinea pigs. The census of nonhuman primates is about 6,000 and the census of nonprimates is about 3,000.



The physiological similarities between nonhuman primates and humans make nonhuman primates useful models for a broad range of disease-related phenotypes. The department provides research support and collaboration on a large variety of projects that use nonhuman primates to study human health-related disease processes. Research projects are directed at problems of infancy and childhood (immediate and long term effects of premature birth, maternal-fetal passive immune transfer, and neonatal programming); adolescence and adulthood

(atherosclerosis, dyslipoproteinemia, hypertension, obesity, type II diabetes, and endometriosis); and senescence (osteoporosis, osteoarthritis, sarcopenia, immune deficiency, and age related reproductive changes). Projects are also directed at infectious diseases such as AIDS, hepatitis, and West Nile virus and potential therapies.

Scientists who are members of the department such as Dr. Linda Brent, Dr. Erika Honore, and Dr. John

McCarrey direct some of these projects. Most projects are directed by scientists in other departments at the Foundation or by scientists at other institutions, including universities and commercial companies. One of the highlights of the department's research programs has been the discovery that the baboon model of human premature lung disease develops lesions in the brain that are very similar to those that develop in very premature humans. The promise is that the baboon model may help researchers understand the nature of premature human cerebral injuries that may contribute to neurobehavioral deficits that are identified as some of these children reach school age. The discovery was a result of work by scientists in San Antonio, Texas; Melbourne, Australia; St. Louis, Missouri; and Boston, Massachusetts.

Several construction projects have been funded

for facilities construction or renovation. Two of these provide additional housing for nonhuman primates. One is to renovate existing housing space, and another is to renovate facilities so that we can expand our work in the area of infectious disease. These projects will improve our ability to house nonhuman primates and support infectious disease research at the Foundation.

Doctoral Staff

(as of February 2003)

Chairman

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

Associate Chair Director, Animal Resources

Larry B. Cummins, D.V.M.

Scientist

Gene B. Hubbard, D.V.M.

Veterinarians

Kathleen M. Brasky, V.M.D., M.S.

M. Michelle Leland, D.V.M.

Associate Veterinarian

Patrice A. Frost, D.V.M.

Assistant Scientist

Linda Y. Brent, Ph.D.

Staff Scientists

Karen S. Rice, Ph.D.

Erika Honore, D.V.M., M.S.

Jera Pecotte, Ph.D.

Postdoctoral Scientist

Massimo Bardi, Ph.D.

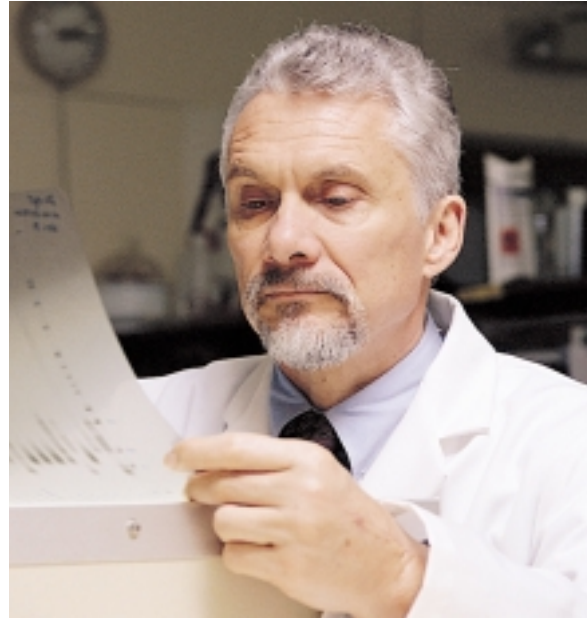


When the Southwest National Primate Research Center (SNPRC) was established at SFBR in 1999, it became the eighth primate center in the United States and the only one in the Southwest. As such, it serves as a resource not only for Southwest Foundation but for research collaborators around the country.

The National Institutes of Health (NIH) supports the national primate research centers to advance the development and utilization of nonhuman primate models for research on human disease. Its base grant to the SNPRC provides funds for physical and administrative infrastructure and primate research, for research services that facilitate existing research programs, and for pilot studies that are expected to lead to major new grant awards. As of December 2002, NIH also has awarded the SNPRC nearly \$10 million in grants toward the renovation, improvement and expansion of SFBR's primate research facilities.

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

Through the SNPRC, this animal colony is helping scientists explore a wide variety of health concerns, including common chronic diseases, developmental abnormalities and infectious diseases. At Southwest Foundation, the primate center's support benefits a broad range of research programs. In fact, its 12 Core Scientists, who are part of the SFBR faculty, are distributed among four of the Foundation's five research departments: Comparative Medicine, Genetics, Physiology and Medicine, and Virology and Immunology.



John L. VandeBerg, Ph.D.
Director

But the primate center also serves as a true national resource, collaborating each year with well over 100 investigators around the nation to study a broad range of diseases. In its 2002 annual report to the NIH, the SNPRC highlighted three research programs reflecting the breadth of its efforts to improve human health.

Atherosclerosis, Hypertension and Obesity

Cardiovascular disease remains our nation's number one killer, accounting for approximately 40 percent of adult deaths. Contributors to this disease risk are such pathological conditions as atherosclerosis, hypertension and obesity, all targets of research through a program project titled "Diet and Genotype in Primate Atherosclerosis."

The project examines how genes interact with dietary factors such as cholesterol and fat intake to influence these three disease traits. In this effort, the

project relies on data obtained from SFBR's large pedigreed families of baboons, whose carefully constructed family trees go back six generations. This, coupled with the ability to carefully control the animals' diet, provides a powerful tool for learning how genes and diet interact to influence disease. Another invaluable tool for this research is the baboon gene map, developed in part under support from this project.

A major accomplishment reported during 2002 was the development of a powerful new method for identifying disease-causing genes. Integrating established genetic screening techniques, pedigree data, information from the Human Genome Project, and an innovative use of microarray technologies – where scientists looked at the expression of many genes, both known and novel, all at once – SFBR researchers have been able to narrow in quickly on a gene on chromosome 18 that helps regulate levels of



HDL cholesterol (good cholesterol) in the blood. When this particular gene is found, scientists will be able to study its mechanism of action and hopefully determine how it might be manipulated by conventional drug therapy or by genetic method.

Encouraging to researchers is the fact that this novel research method drastically reduces the amount of time and money needed to identify disease genes. And while it currently is being applied to research with baboons in the hunt for a gene that regulates HDL cholesterol, the strategy is applicable to any species where a trait has been mapped to a chromosomal region and can be utilized in the study of numerous diseases.

Salt-Sensitive Hypertension

While it has been known for some time that a defect in kidney function can cause the high blood pressure disease state known as hypertension, research with both animal models and humans has shown that there also is a genetic contribution to this disease process. Patients who have a family history of hypertension have an increased level of a cell membrane sodium transport characteristic known as sodium-lithium countertransport (SLC) activity. Thus, they experience large increases in blood pressure in response to increased consumption of salt in their diets. Since there is substantial genetic control of SLC activity, it is believed that the same genetic factors might produce inherited forms of hypertension.

Until recently, there have been no animal models available for studying the physiologic mechanisms that regulate SLC activity and how these factors may be related to the dysregulation of blood pressure.



However, research by scientists at Southwest Foundation and the SNPRC has shown that SLC activity in baboons is identical to that of humans, and the majority of SLC activity in the baboon is influenced by a single gene located on chromosome 4. This discovery offers the opportunity to study the relationship between several factors known to be important in sodium metabolism in baboons with high and low SLC activity.

Supplemental research will test the hypothesis that high SLC activity produces an inappropriately high level of a hormonal system, the renin-angiotensin-aldosterone system (RAAS), and that high levels of RAAS promote salt retention by the kidneys and a sodium-dependent increase in blood pressure that ultimately results in hypertension.

Protective Immunity to Hepatitis C

Chronic infection with hepatitis C virus (HCV) affects an estimated 3 percent of the worldwide population and is the leading cause of liver failure and liver transplantation. It also accounts for 25 percent of all hepatocellular carcinoma cases. Consequently, there is a critical need to develop vaccines against the virus, but until recently, the numerous obstacles to vaccine development proved to be very discouraging. In fact, early studies suggested that once an individual had cleared HCV infection, little to no protective immunity existed that would safeguard that individual from reinfection with the virus.

Recently, however, scientists at Southwest Foundation and its Southwest National Primate Research Center have found reason for hope through a successful study with chimpanzees. As the only animal besides man that is susceptible to HCV infection, the chimpanzee does not develop disease from the infection. This makes the chimpanzee an extremely important animal model for vaccine development, especially since no tissue culture system for HCV exists to aid in this effort.

Doctoral Staff

(as of February 2003)

Core Scientists

John L. VandeBerg, Ph.D., Director
Department of Genetics
Suzette D. Tardif, Ph.D., Associate Director
Department of Physiology & Medicine
Jonathan Allan, D.V.M.
Department of Virology and Immunology
K. Dee Carey, D.V.M., Ph.D.
Department of Comparative Medicine
Larry B. Cummins, D.V.M.
Department of Comparative Medicine
Bennett Dyke, Ph.D.
Department of Genetics
Gene B. Hubbard, D.V.M.
Department of Comparative Medicine
Robert E. Lanford, Ph.D.
Department of Virology and Immunology
Luis D. Giavedoni, Ph.D.
Department of Virology & Immunology
Karen S. Rice, Ph.D.
Department of Comparative Medicine
Jeffrey A. Rogers, Ph.D.
Department of Genetics
R. Mark Sharp, Ph.D.
Director of Biostatistics & Scientific Computing

Postdoctoral Scientist

Darlene A. Smucny, Ph.D.

In 2002, Foundation scientists demonstrated that chimpanzees that had cleared infection with one strain of HCV showed protective immunity against different forms of the virus. This offers the first evidence that an effective HCV vaccine might be possible.

The resources of the SNPRC have been critical to this successful research effort since the primate center is one of only a handful of places with a chimpanzee colony and the facilities and expertise to conduct research on infectious disease with these animals.

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Scientists Find New Target for Blocking HIV

An article in the December issue of the *Journal of Virology* highlighted some hopeful findings related to AIDS research by Dr. Jason Kimata and his colleagues in SFBR's Department of Virology and Immunology. In their article "Capture and Transfer of Simian Immunodeficiency Virus by Macaque Dendritic Cells is Enhanced by DC-SIGN," the group shared research results showing that a lectin-binding protein known as DC-SIGN, though necessary to immune function, binds to HIV and spreads it to T cells, or target cells. In this way, a protein that is supposed to assist the body's immune system actually amplifies HIV infection. It is hoped that this new knowledge might lead to effective treatments or preventions. If scientists can design strategies to block the binding of HIV to this protein, they may be able to thus block the amplification of infection and the spread of HIV. Since Dr. Kimata's group discovered that simian immunodeficiency virus (SIV), which causes AIDS in macaque monkeys, also uses the DC-SIGN protein to spread infection, the SIV macaque model of AIDS may be useful for testing experimental therapies that block viruses binding to DC-SIGN.

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Hormone Antagonist Could Help Patients with Congestive Heart Failure

New evidence published by Dr. Robert Shade and his colleagues in the Department of Physiology and Medicine has shown that a hormone regulating salt appetite may worsen congestive heart failure. The article, which appeared in the *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*, showed that salt intake behavior in baboons can be enhanced by increasing peripheral levels of the steroid hormone aldosterone. Researchers believe the hormone is a normal regulatory mechanism for increasing salt appetite when the body is in a low-sodium condition; however, levels of the hormone also are elevated in patients with congestive heart failure. In these situations, the hormone's effect would worsen the patient's condition by promoting salt and water intake in excess of what the body needs. Work by Dr. Shade and his colleagues thereby supports recent evidence suggesting that the blockade of mineralocorticoid hormones such as aldosterone during congestive heart failure should be therapeutic.

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Novel Compounds Show Activity Against Cancer Cell Lines and Tumors

The December 2002 issue of *Steroids* featured an article highlighting the synthesis of some novel compounds developed by Dr. Pemmaraju N. Rao, senior scientist and chair of the Department of Organic Chemistry, as well their biological activity against cancer cell lines and tumors, as demonstrated through a collaboration with Dr. Susan Mooberry and her colleagues in the Department of Physiology and Medicine. The compounds are derivatives of 2-methoxyestradiol (2-ME2), a natural metabolite already being evaluated against cancer in multiple Phase I and Phase II human clinical trials across the country. *In vitro* and *in vivo* research conducted at SFBR revealed that three of the derivatives showed advantages over the parent compound, 2-ME2. The compound 14-dehydro-2-ME2 was shown to be 6 to 15 times more potent than the natural metabolite for inhibiting endothelial cell activities, which may prevent tumor growth. It also was shown to be 15 times more potent than 2-ME2 for cytotoxicity, or ability to kill specific types of cancer cells, and it showed a demonstrated advantage against breast cancer in the mouse model. The compound 2-ME2-15 α ,16 α -acetonide showed a demonstrated advantage against breast cancer in the mouse model, and 15-dehydro-2-ME2 showed a demonstrated advantage against prostate cancer when tested *in vitro*.

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Baboon Proves to be Promising Model for Alzheimer's

Dr. Gene Hubbard, scientist in SFBR's Department of Comparative Medicine, co-authored a paper in the journal *Interdisciplinary Topics in Gerontology* revealing that the baboon is a promising new model for research on Alzheimer's and similar diseases. Through studies with SFBR's own animal colony, scientists have found that some baboons accumulate abnormal tau proteins in the brain, causing impaired brain function. This same pathology is found in human patients who suffer from Alzheimer's disease, as well as related diseases like Pick's disease, progressive supranuclear palsy, and argyrophilic grain disease. It also occurs in hereditary conditions known as frontotemporal dementia and Parkinson's disease linked to chromosome 17. This genetic link underscores the significance of tau dysfunction to the development of neurodegeneration and dementia in humans. Now that a similar pathology has been found in baboons, scientists hope this new animal model will provide valuable information not yet available from human studies on these devastating diseases. With its unique pedigreed baboon colony, where family groups have been monitored for six generations, SFBR in particular is in a good position to study genetic influences on these diseases, hopefully leading to early diagnosis and better treatments.

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First Evidence of Genetic Susceptibility to Roundworm Infection

Dr. Sarah Williams-Blangero and her colleagues in the Department of Genetics have provided the first clear evidence for a genetic contribution to susceptibility to infection with roundworm (*Ascaris lumbricoides*). Roundworm infection is a major global health problem, affecting a quarter of the world's population. The consequences of infection are particularly severe in young children due to its association with deficits in growth and development. While it has been well recognized that roundworm infections tend to aggregate in families, until now little was known about the possible genetic determinants of susceptibility to infection. In 2002, Dr. Williams-Blangero's research with a Nepalese population determined that two individual genes influence susceptibility to infection with roundworm, a result which was published in the *Proceedings of the National Academy of Sciences*. Dr. Williams-Blangero and her colleagues have mapped these genes to small regions on chromosomes 1 and 13, and research is now underway to identify them. Knowledge of the specific genes involved can be used to suggest new pathways to be targeted in drug development efforts directed at improving the treatment and prevention of helminthic infections.

