Building a Brighter Future

2003 Report of Progress

SFBR

Southwest Foundation
for Biomedical Research

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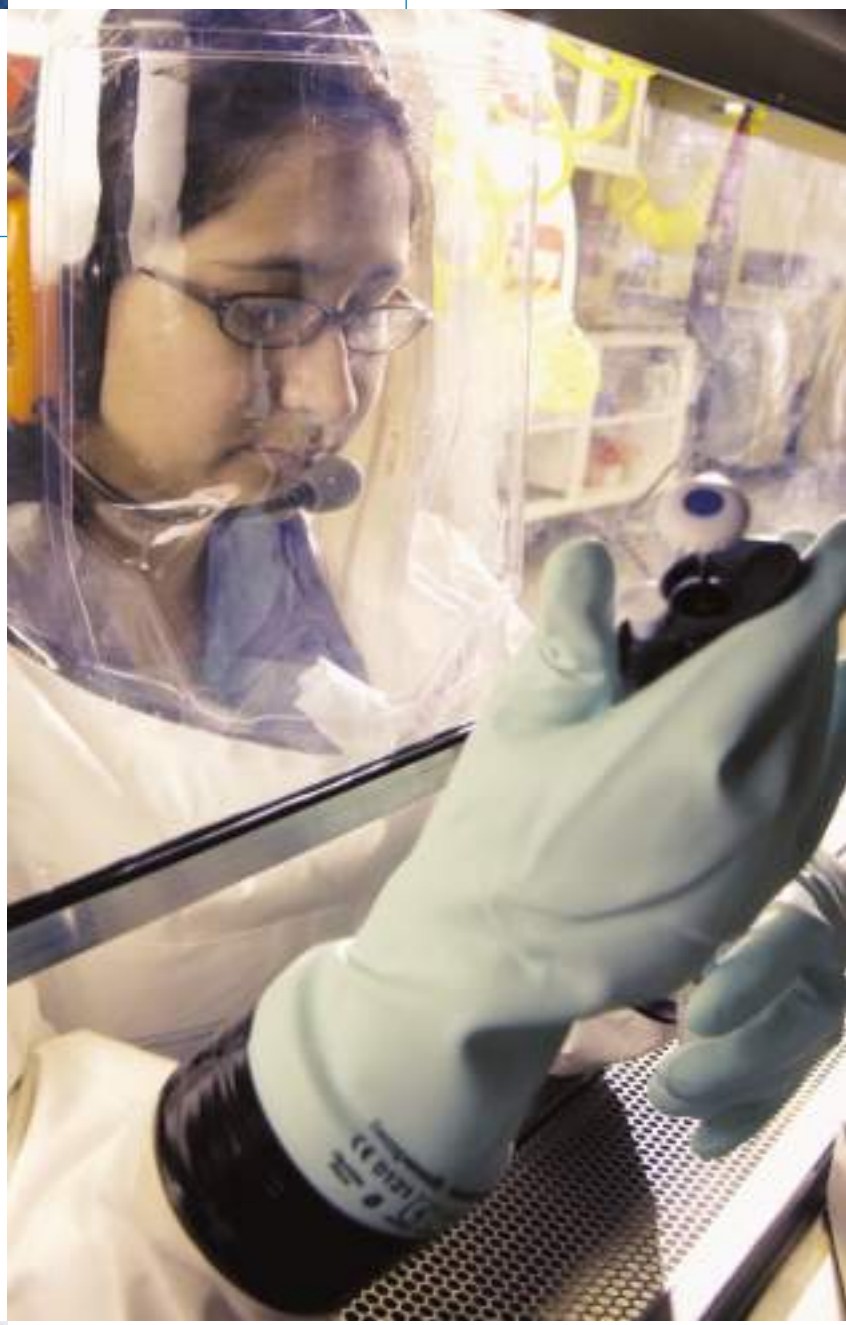
Building a Brighter Future



Progress achieved at SFBR in 2003 occurred on two fundamental levels. While Foundation scientists continued to forge ahead in their quest to find new preventions, treatments and cures for disease, the Foundation also made great strides in its efforts to better equip its scientists for their important endeavors.

The year marked a peak in a campus modernization plan developed in the mid-1990s, with 19 separate construction projects at various stages of planning or completion in 2003. A combination of vital philanthropic support and federal construction grants allowed SFBR to move ahead with critical campus improvement projects that included new scientific offices and laboratories, new and renovated animal facilities, and the dedication of the acclaimed SBC Genomics Computing Center, all for the purpose of improving human health and saving lives.

In this Report of Progress, we invite our readers to see how the work of construction crews and brilliant scientists are being combined to help build a brighter future for us all.

Letter from the President

The 2003 year at SFBR was all about building a brighter future for human health.

As our scientists continued to excel in their search for scientific discoveries that could lead to new methods of prevention and treatment of disease, we also made great strides in our plans to provide them with state-of-the-art facilities that better enable them in this effort.

Through steadfast support from our philanthropic donors and sponsors such as the National Institutes of Health, we had 19 separate construction projects at various stages of planning or completion in 2003. This momentum began in the late 1990s and now reaches its zenith with more than $50 million being invested in our research facilities. This result is awesome, and it would not have been possible without the total team effort of all our leadership. I would like to recognize the campaign committee chaired by the dynamic John Kerr. The SFBR Trustees led by example, contributing a staggering $22 million of this total. It is clear that philanthropy enabled SFBR's founding more than 60 years ago, and it is philanthropy that sustains us today. We are grateful to so many whose gifts have literally built this institution.

In the ensuing chapters of this report, which detail the many projects that have materialized to date, you can see just how far the Foundation has come in caring for the needs of our research scientists and our invaluable animal colonies. You also can see, from our construction update and from our scientific reports, how these campus improvements contribute to the outstanding achievements of our faculty, and ultimately to the health and well-being of us all.

As someone who has been heavily involved in our Campus Modernization Plan during my 12-year tenure at SFBR, it has been personally fulfilling to see the progress of the Foundation in this arena. I would like to commend Mr. Lee Bricker, director of facilities, and Dr. Gregory Patterson, associate scientific director, for their leadership and oversight of this extraordinarily complex construction and modernization effort. The

results are a source of pride for all of our faculty and staff, as well as for the many friends and supporters who placed this progress within our grasp.

I also want to take this opportunity to thank Dr. Robert Shade, who for the past four years served as the Foundation's scientific director. After steering us through some of the most successful years in the Foundation's history, he has stepped down from this position so that he can devote more of his time to his extensive research program. We are grateful for his contributions to the success of our organization.

In early 2003, SFBR initiated a search for a new scientific director, an 18-month process that has culminated in the recruitment of Dr. Philip LoVerde, a SUNY Distinguished Professor in the School of Medicine and Biomedical Sciences at the State University of New York at Buffalo and a world-renowned authority on schistosomiasis. He will join our faculty in 2005 upon the completion of his laboratory facility. Until that time, Dr. William Stone, who for many years was the Cowles Distinguished Professor of Biology at Trinity University, is serving as the interim scientific director. SFBR is truly fortunate to have the services of these distinguished scientists at the helm of our scientific programs.

In late February 2004, I announced to the Board of Trustees my own plans to retire once succeeded and requested that a search be initiated for my replacement. That search is ongoing, and it is my full expectation that the new president and scientific leadership will take this organization to its next level of excellence.

But now, join me in recognizing the milestone achievements made at SFBR in 2003. I congratulate our scientists and staff on a job well done, and I thank all of the many valued friends and supporters who are helping us build a brighter future for human health.

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Campus modernization effort has large payoff for human health

When you think of tools that help scientists in their research, such things as microscopes, centrifuges, Petri dishes, pipettes and computers usually come to mind. However, some other very important tools of the trade at SFBR in 2003 were concrete and steel, hammers and nails, nuts and bolts, bulldozers and welding equipment.

Although these tools are not used by Foundation scientists, they are critical to the scientists' ability to stay on top of their field as they search for lifesaving advances in biomedical research. That is because these tools are being used as part of a major campus renovation effort intended to replace tired, old buildings with new, state-of-the-art facilities that can help SFBR researchers remain on the cutting edge.

Development of a comprehensive plan

While this campus modernization effort reached its peak in 2003, when the Foundation had 19 separate construction projects at various stages of planning or completion, it got its start in the mid-

1990s. Under the leadership of then-SFBR Chairman George C. "Tim" Hixon and SFBR President Dr. Frank Ledford, the Foundation developed a campus modernization plan meant to carry SFBR successfully into the 21st century and help it maintain its status as a world leader in biomedical research.

"Walking around the campus in the mid-1990s, it was easy to see that many of the Foundation's facilities were getting old," said Mr. Hixon. "Some of the buildings and laboratories were originals constructed when SFBR first moved to its current campus in the late 1950s. So it was evident that, if SFBR was going to continue to attract bright young scientists to its faculty, we needed to provide them with modern facilities in which to work. That is what the campus modernization plan set out to do."

Donors help make plan a reality

Of course, to carry out its modernization plan, SFBR also needed to rely on the goodwill and financial support of many friends and donors. Unlike universities and many hospitals, SFBR cannot depend on state budget financing, patient revenue or tuition to support progressive expansion. Likewise, while grants from the National Institutes of Health could be sought for some construction projects, those grants are fiercely competitive and hard to come by. They also frequently require matching funds.

So SFBR embarked on what would be a more than $50 million capital campaign to improve its campus. An initial campaign was developed to fund a new office and laboratory complex for the growing Department of Virology, which was constructed with a $1.3 million grant from the NIH and more than $11 million in philanthropic support.

Dedicated in 1999, the Betty Slick and Lewis J. Moorman Jr. Laboratory Complex is a 34,000 square-foot facility that allowed all of the Foundation's virologists – who had been spread out in various buildings around campus – to come together under one roof. It also better equipped them to advance their understanding of infectious diseases and the immune system, and to develop new vaccines and therapies.

In addition to its scientific offices, con-

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ference rooms, and traditional biosafety level 2 and 3 laboratories, this new facility put SFBR on the map with a biosafety level 4 (BSL-4) laboratory. One of a handful of operating BSL-4 labs in the country and the only one that is privately owned, this maximum containment laboratory offers SFBR scientists the safest environment in the world to study deadly infectious diseases for which there are currently no treatments or vaccines. As such, it has helped propel Foundation scientists into a leading role on research related to biodefense and emerging infectious diseases.

After the completion of the new virology complex, SFBR launched an ambitious $40.3 million capital campaign to support remaining initiatives in the campus modernization plan, to support faculty recruitment, and to build up SFBR's endowment.

Chaired by John Kerr, who became SFBR's chairman in 1998, this campaign is now essentially completed and is well on its way to making a tremendous difference in the daily work of SFBR scientists.

"The completion of this program was possible only as a result of major philanthropic gifts that the Foundation was fortunate to receive, including very generous support from its own Board of Trustees and from major foundations, both in San Antonio and elsewhere in the region," said Mr. Kerr. "We owe a great debt of gratitude to the many donors who have helped us complete our capital campaign. Thanks to their contributions, we are modernizing our campus and building world-class facilities for our scientists, which ultimately will benefit all people through improved medical care that results from their research."

SFBR Chief Development Officer Corbett Christie echoed Mr. Kerr's gratitude to campaign donors, offering special acknowledgement to the Board of Trustees. "One of the signs of a strong organization is how well its own governing board supports its strategic projects," said Mr. Christie. "Our trustees have

SFBR Campus Modernization Timeline

1995

SFBR Campus Modernization Plan developed

April 1999

Betty Slick and Lewis J. Moorman Jr. Laboratory Complex dedicated

accounted for more than $20 million of our $40.3 million goal. A more impressive example of support cannot be found, in my experience. This is a board that leads its own projects."

In 2003, funds from the capital campaign were coupled with NIH grants to help SFBR make a large leap forward in its campus renovation effort. New offices, laboratories, and a state-of-the-art genomics computing center have been constructed to help SFBR scientists remain pacesetters in the race for genetic discovery. New animal facilities have been added to the campus, and others are scheduled for renovation to ensure a high quality of life for SFBR's growing animal colonies. And infrastructure improvements have been made that may not be visible to visitors, but they are vital to the day-to-day operations of the campus. These improvements are highlighted in the following pages.

March 2000

The nation's only privately owned maximum containment laboratory "goes hot" at SFBR

Summer 2000

$40.3 million "Campaign for Southwest Foundation" initiated

June 2003

SBC Genomics Computing Center dedicated

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Technology for life: SFBR dedicates the SBC Genomics Computing Center

On June 18, 2003, SFBR's statistical geneticists felt like "...children who have popped downstairs on Christmas morning and found this wonderful gift, a gift that will change lives remarkably," said Dr. John Blangero, leader of the group.

Dr. Blangero was one of a distinguished list of speakers at dedication ceremonies held that day for the new SBC Genomics Computing Center. The 6,741-square-foot center is a high-tech addition to the SFBR campus that brings its stellar group of statistical geneticists together in one office complex. More importantly, however, it has allowed the Foundation to increase dramatically the power of its famed parallel computing network known as the "computer ranch." As a result, SFBR is now home to the world's largest computer cluster devoted to statistical genetic analysis, and its scientists can search for disease-influencing genes at record speed.

What is a computer ranch?

The computer ranch is a parallel computing network that converts a group of traditional desktop computers into a supercomputer for genetic research. First con-

SFBR Campus Modernization Timeline

June 2003

SBC Genomics Computing Center dedicated

Fall 2003

Various new facilities for baboon social housing are completed

ceived and implemented by SFBR scientists Dr. Bennett Dyke, Dr. John Blangero and others in the late 1980s, the network allows investigators to partition complex genetic analyses across multiple computers in order to reduce the time required for assessing the genetic components of susceptibility to disease. With each processor that is added to the network, the computing power and speed of the entire network increases.

The need for this sort of resource is more clear when one considers that there are 3 billion base pairs of DNA in the human genome, and in their various research projects, SFBR scientists are conducting gene scans of some 13,850 individuals in eight populations as they search for genes influencing a variety of diseases. "We have to sift through all of that information and find the specific errors, the changes in DNA, that lead to increased disease risk," explained Dr. Blangero.

Dr. Sarah Williams-Blangero, chair of SFBR's Genetics Department, added, "We're generating a huge volume of data, and the speed at which we can analyze that data is limited only by the computing resources available."

New center allows for dramatic expansion

Before the SBC Genomics Computing Center was constructed, SFBR scientists had built up their computer ranch to 200 dual-processor computers – the equivalent of 400 traditional computers – housed in

December 2003

Phase II completed; scientists occupy new offices and molecular genetics laboratories

Spring and Summer 2004

New long-term chimpanzee housing and other animal facility upgrades completed

June 2004

Capital campaign officially surpasses its $40.3 million goal

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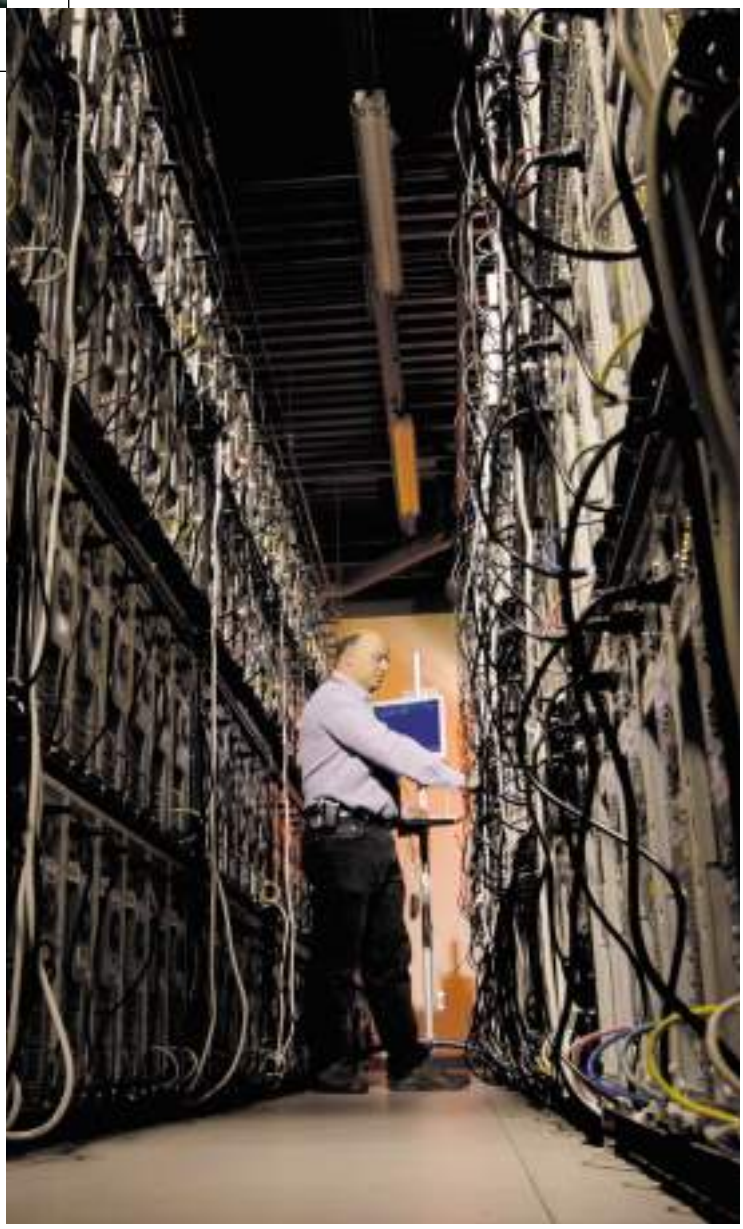
two separate buildings on campus. This was an advance in itself, reducing the time of a typical genetic analysis from one month to two weeks.

SFBR scientists had the vision to expand the ranch and increase its speed even further. Organizations such as the National Institute of Mental Health and Australian-based AGT Biosciences even provided funding for more computers. The problem, however, was that the Foundation did not have a facility large enough or with adequate power and air-conditioning systems to house a larger network.

That problem was overcome when the SBC Foundation, the charitable giving arm of San Antonio-based SBC Communications Inc., provided $1 million as the lead gift for a new, state-of-the-art facility to house the computing network. David and Jean Monnich followed suit with a major donation of structural steel



SFBR Campus Modernization Timeline

First Quarter of 2005

Phases III & IV of campus modernization scheduled to begin; dramatic renovations planned for genetics laboratories and offices and for the Preston G. Northrup Memorial Library, including the addition of the Leroy G. Denman Jr. Atrium

Spring 2005

Expected completion of new scientific director's laboratory; renovation of animal clinic and other animal care facilities scheduled

2005...

SFBR continues ongoing efforts to modernize its campus

for the building, and by the summer of 2003, the new facility was a reality.

With the new SBC Genomics Computing Center, SFBR has been able to expand its computer ranch to include 1,500 processors, with room to add more in the future. Consequently, the complicated analyses that used to take a month now take just minutes.

"The center thus enables a dramatic increase in speed with which scientific discoveries will be made," said Williams-Blangero.

SFBR's genetic research has global impact

Currently, the computer ranch is used by SFBR investigators to search for genes influencing common complex diseases such as heart disease, diabetes, obesity, osteoporosis, psychiatric disorders, and parasitic infections. Of course, the parallel computing network and the SFBR-designed analytical software that takes advantage of its capabilities, known as SOLAR, can be used to study any type of disease that has a genetic influence.

"And because our department collaborates with more than 200 researchers at 80 institutions around the world, this new center is sure to benefit projects on a global level," Williams-Blangero said.

In fact, SFBR officials expect that this unique, powerful application of technology will lead to additional collaborations, the recruitment of new faculty, and an enhanced ability of SFBR geneticists to generate NIH and industry support for new research projects. The ultimate payoff, though, will be to human health.

"Once the specific genes influencing a disease are identified, this genetic information can be used in drug development efforts to find more effective cures or methods of prevention of disease," said Williams-Blangero.

Others praise this technological advancement

Dr. Steve Moldin, director of the Office of Human Genetics and Genomic Resources for the National Institute of Mental Health, had high praises for the new computing center and the people who utilize it, "When you have a tremendous resource such as this that is so powerful and couple it with key staff like you have at SFBR – staff who have international collaborations and an international reputation as a stellar team of leaders in the field of statistical genetics – you are certain to advance by leaps and bounds our understanding of complex diseases."

Dr. Raymond White of the University of California, San Franciso, whose landmark paper in 1980 established the basis for the genome scanning approach to assessing the genetic components of susceptibility to common diseases, echoed Dr. Moldin's sentiments. He said, "This computational power provides not only the potential for enormous contributions to our study of human genetics and human disease processes at a molecular level, but it also provides the power to keep SFBR, San Antonio and the SBC Genomics Computing Center at the forefront of what is going to be a wave of new discovery. There are so many genetic discoveries that already have been made, but those really are just the tip of the iceberg. There is an avalanche of new understanding that is going to come from this effort."

SBC Communications President of External Affairs John Montford said that SBC is proud to be an important partner in such an innovative project. "There are so many discoveries waiting to be made, and now those discoveries are within our grasp. SFBR is in the best position anywhere in the world when it comes to capitalizing on the promise of the Human Genome Project. Scientists here will help people around the globe live longer and enjoy an improved quality of life. That is something we can all take pride in."

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SFBR Campus Modernization – Phase II sees completion

Geneticists move into new facilities

The year 2003 was an important one for SFBR's Department of Genetics. Six months after dedication ceremonies for the SBC Genomics Computing Center, the new Molecular and Biochemical Genetics Laboratories made their debut.

With the completion of Phase II of the SFBR Campus Modernization Plan in December 2003, the majority of SFBR geneticists have moved into new laboratories that better facilitate their research, thanks to the generosity of the foundations, corporations and individuals who contributed to SFBR's recent capital campaign, as wells as a $1 million grant from the National Institutes of Health.

A difference of night and day

Gone are the laboratories and offices in the back portion of the Tom Slick Memorial Building and the Urschel Memorial Research Laboratory, a complex originally constructed in the late 1950s and early 1960s. Reconstruction of the building's interior that began in August 2002 included the demolition of the old, windowless lab space with its labyrinth interior, dead-end corridors, and power that could not keep up with the demands of modern laboratory equipment.

In its place now is more than 20,000 total square feet of new, state-of-the-art laboratories in the Robert J. Kleberg Jr. and Helen C. Kleberg Wing and the Ewing Halsell Wing, as well as office space for scientists and technical staff in the Franklin Family Scientific Pavilion. More than being simply new, the renovated space is designed for greater efficiency with more usable workspace for scientists. The building's infrastructure also has been upgraded to meet modern power and safety standards.

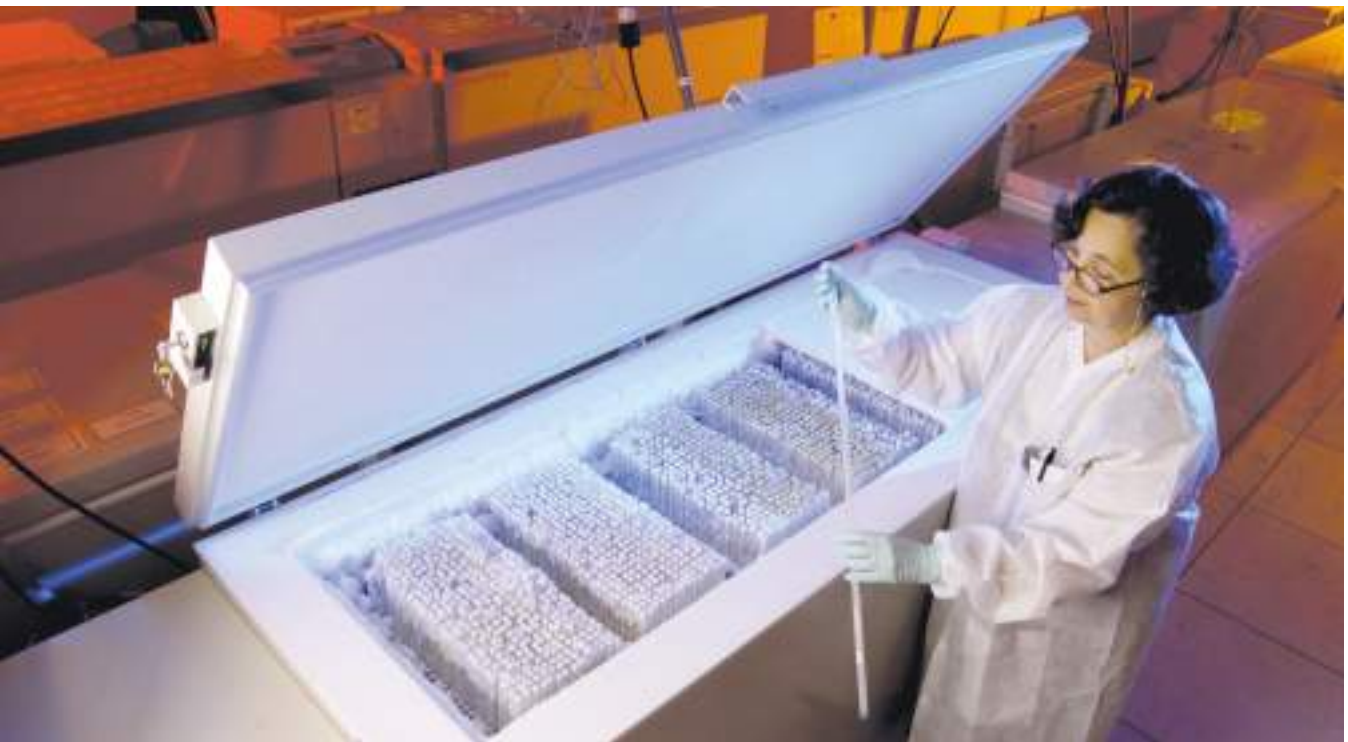
Scientists appreciate their new facilities

Scientists using the new facilities could not be happier. For Dr. Laura Cox, the renovation means that she and her technical staff finally have their own laboratory. "In the past, I was borrowing lab space from another scientist," she said. "So the facility upgrade is a definite advantage for us, allowing us to organize our lab space based on the types of experiments we need to do. In addition to that, all of the new labs are well laid out, with a lot of very practical workspace for the scientists. And everyone appreciates the windows that have been added to the laboratories. It's nice finally to have natural light, which I think is good for our emotional health more than anything else."

In addition to the improved layout and design of individual laboratories, Dr. Shelley Cole says the building itself is designed in a more efficient manner that fosters collaboration. She explained that scientists' laboratories are located around the perimeter of the building, with shared resources located in the building's center. "That gives us easy access to everything we need to do our jobs," she said.

Dr. Cole added, "It's also very beneficial for the Genetics Department to have most of its faculty together in one building rather than spread out all over campus. It allows us to see each other more often, share each other's resources and share ideas. That stimulates collaboration and cooperation."

One member of Dr. Cole's research group, Lucien Costley, said he appreciates that the lab is simply new. "New facilities boost employee morale," he explained. "We want to work even harder at our research because now we're in a cutting-edge facility that is designed not for the needs of scientists 30 years ago, but for the work we're doing today."



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Animal colonies benefit from new and renovated facilities

SFBR scientists are not the only ones benefiting from the Foundation's campus modernization efforts. So are its primate colonies. With grant support from the National Institutes of Health and matching funds from SFBR, the Foundation is in the process of building and renovating a number of facilities to meet the needs of its growing colony of nonhuman primates.

"The modernization of existing primate facilities and the construction of new facilities proceeded during 2003 at a pace unprecedented in the history of the Foundation, thanks to NIH grants awarded as a consequence of the establishment of the Southwest National Primate Research Center in 1999," said Dr. John VandeBerg, director of the primate center. "These upgrades and expansions will enable the SNPRC, already a national resource, to make even greater contributions to research based at SFBR and at many other institutions around the country."

Dr. VandeBerg added that the facility upgrades and additions are good for the animals as well as for science. "They allow us to provide the animals with excellent housing conditions conducive not only to high standards of health and maintenance, but also to the animals' psychological well-being. That is in keeping with our commitment to the humane care and treatment of the animals, as well as to high quality scientific research, which go hand in hand."

New and renovated housing for baboons

In October 2003, some of the Foundation's baboons moved into nearly 8,500 square feet of new social housing dubbed the "F Cages." This new animal facility, built to house animals in social groups, provides additional indoor-outdoor housing for the expanding baboon colony. While these cages can be used for animals of any age, SFBR's chief veterinarian and chair of the Department of Comparative Medicine, Dr. K. Dee Carey, says they will be especially good for aged animals. "These new cages provide a more efficient and protective environment for the animals than some of our older cages," he explained. "The outdoor portion of the F cages provides more shade and shelter from the weather, which will be good for the animals on hot summer days. Likewise, the indoor portion of the housing has a heating system that is even more effective than that of our older cages, which will benefit the animals on cold winter nights. Since the older animals tend to be more fragile than the others, the F cages – as well as the similarly constructed E cages – are ideally suited for them."

Currently, some of the F cages, as well as additional "swing space" housing completed in December 2002, are being used temporarily for some baboons assigned to social housing known as the B, C, and D cages while those facilities are being renovated. One section at a time, workers are going over this 56,000 square feet of housing to repair or replace damaged fencing, redo cage floors, make plumbing repairs, and ensure that heating systems are adequate. New shower and locker facilities also are being constructed for the dedicated staff who care for these animals.

All of these improvements are vital to the welfare of the Foundation's baboons, which because of their similarity to humans in genetics and physiology make natural models for studies on heart disease, diabetes, obesity, osteoporosis, osteoarthritis, menopause, parasitic diseases, problems of premature infants, and many other maladies that affect humans.

Enhancement to "Chimp Village"

Like the baboons, many of the chimpanzees at SFBR also are enjoying new or improved housing thanks to campus improvements completed or begun in 2003. Chimpanzees are critical to many areas of research, particularly those related to AIDS and hepatitis C. The only animal besides man that is susceptible to infection with HIV or hepatitis C, the chimpanzee does not develop disease from either infection. This makes chimpanzees ideally suited for trials on candidate vaccines or drug therapies against these viruses, which can prove deadly in humans.

Through most of 2003 and the early part of 2004, construction was completed on the huts, or small apartments, that house chimpanzees involved in studies on these infectious diseases. While it is important to keep the animals separated so they do not share infections and invalidate a study, it also is important for these animals to have social interaction, a chance to be outdoors, and as much space as possible for exercise.

The recent renovation to "Chimp Village" included the addition of outdoor cages, or runs, to each of the huts. This gives the chimpanzees access to the outdoors, more room to run and climb, and auditory-visual contact with other chimpanzees in nearby huts.

"The outdoor runs added to the huts in Chimp Village have greatly contributed to the well-being of the chimpanzees housed there," said Dr. Christina Grassi, director of behavior and enrichment for the Department of Comparative Medicine. "They're in a more

dynamic environment that allows more sociability, and it's evident that they really enjoy the outdoor exposure. Every morning when I arrive at the Foundation, I can see a chimpanzee sitting on almost every high perch, watching the other chimpzees as well as all the hustle and bustle of people on the SFBR campus."

Domes of their own

Other chimpanzees that are off research protocols for six months or longer have recently moved or are in the process of moving to brand new long-term housing facilities. Nearly 14,300 square feet of indoor and outdoor chimp housing has been added to the SFBR campus, including 12 Primadomes™, which are large, domed, outdoor enclosures that create a spacious and interesting environment for the animals to explore.

The Primadomes™ contain playground equipment, poles for climbing, heavy-duty perches at various heights, and a number of other features designed to encourage physical exercise and mental stimulation. "The chimps can perch, relax, run, climb and arm-swing at a variety of heights," Dr. Grassi said. "So the variety of structures we've placed in the Primadomes™ allows not only for complex locomotion, but it also stimulates more complex behaviors."

Each Primadome™ also is connected to runs leading to four indoor enclosures. "This gives the chimpanzees the opportunity to be inside and protected from the weather or outside in what can be described as an environmentally rich setting," said Dr. Carey. "Another benefit of this new long-term housing area is that it allows us to keep chimpanzees in larger groups, which is good for the animals' sociability."

Other campus improvements in 2003

As with any major campus renovation, SFBR's modernization efforts have included infrastructure improvements that are invisible to passersby but nonetheless necessary to sound operations. For example, two projects were undertaken in 2003 that added eight new generators to the campus. The generators will provide emergency power to the Foundation's indoor animal housing areas so that, in the event of an extended power outage, the facilities will not lose ventilation or temperature control. In addition, major work began in 2003 on a new sewer line that will allow the Foundation to keep up with the growth in its animal colonies and the new animal facilities that have been added to the campus.

Another project underway is aimed at expanding important scientific research projects on infectious diseases. This work involves the Quarantine Building, where any animals new to the Foundation are housed for a period of time to ensure they are not carrying a disease that would be harmful to other SFBR animals.

A portion of this building is being converted to provide procedure and clinical space, as well as a new facility capable of housing nonhuman primates involved in research on infectious diseases that require biosafety level 3 (BSL-3) containment, such as West Nile virus. This addition will allow SFBR virologists to expand their research related to biodefense and emerging infectious diseases to include vaccine and therapy trials with animals that are similar to humans in their genetics and physiology.

This is important because, in the case of new drugs or vaccines against deadly bioterror agents or emerging diseases, these trials with nonhuman primates might actually replace human clinical trials required by the U.S. Food and Drug Administration for new drugs against common diseases.

"First, it would be unethical to test these new treatments and vaccines in humans with challenge studies," said Dr. Jean Patterson, chair of the Department of Virology and Immunology. "But if researchers gave a person a new vaccine for one of these agents and waited for them to be exposed in nature, it could take years or even decades to prove the vaccine's efficacy. For these reasons, the FDA has ruled that new treatments and vaccines in the biodefense effort can forgo traditionally required human clinical trials if they prove safe and effective in two animal models. If one of these new treatments does prove safe and effective in animals, the drug can then be stockpiled for use in the event of a national emergency."

Dr. Suzette Tardif, associate director of the Southwest National Primate Research Center, explained why it is important for one of those animal models to be a nonhuman primate. "Because these animals' genetics and physiology are so much like our own, it is reasonable to assume that a drug that proves safe and effective with nonhuman primates will also be safe and effective in humans," she said.

This makes the Foundation's new animal BSL-3 facility a small addition to the SFBR campus that could have a big impact on human health.

Building a Brighter Future

Improvements still to come

With all of the improvements made to the SFBR campus in 2003 and preceding years, more crucial additions and renovations are being planned for the near future.

Continued upgrades to the Foundation's animal facilities are in the works. The main clinical care area for the pedigreed baboon colony is scheduled for renovation, as is the building that houses the Foundation's cage-washers and centralized cage-washing facilities. The Foundation also is preparing to break ground on a $2 million project to build new indoor-outdoor housing for SPF (specific pathogen free) rhesus monkeys, which provide an invaluable animal model for AIDS research.

Completion of upgrades for the Genetics Department

The largest and perhaps most anticipated remaining project, however, is the execution of Phases III and IV of the Foundation's Campus Modernization Plan, made possible by donations to SFBR's recent capital campaign and $3 million in grants from the National Institutes of Health. Just as Phase II involved a complete overhaul of the rear portion of the Slick-Urschel Laboratory Complex, so Phases III and IV, scheduled to begin in the first quarter of 2005, will focus on the front portion of the same complex.

Approximately 40,000 square feet of the building's interior will be gutted and completely rebuilt to include six new state-of-the-art genetics laboratories, office space for scientists, a new departmental office for the Genetics Department, and new conference rooms. The area also will feature the Leroy G. Denman Jr. Atrium, made possible by the successful matching of a challenge grant from The Tobin Endowment. Complete with various sitting areas as well as a skylight and glass walls to draw in natural light, the atrium will provide a pleasant and relaxed meeting space for scientists and other Foundation staff.

Coupled with the Phase II renovations and the construction of the SBC Genomics Computing Center in 2003, the planned Phase III and IV renovations will complete the Foundation's effort to bring all of its geneticists together in a centralized location and equip them with modern laboratories that better facilitate their cutting-edge research.

Dramatic changes to the library

In addition to these improvements for the Genetics Department, Phases III and IV of the campus modernization effort also will include a major renovation that will benefit the entire campus: a redo of the Preston G. Northrup Memorial Library to the beautiful standard set in the Kathleen L. and Robert M. Luby Library Atrium, a gift of Mrs. Robert Luby in honor of her husband.

The renovated facility will offer space for individual private study, a separate working space for group collaborations, as well as a lounge area. Underneath the general design and aesthetic changes, there also will be a number of infrastructure improvements. For example, network data connections and electrical outlets will be added throughout the library, allowing SFBR scientists and their collaborators to connect their laptop computers to the SFBR network and the Internet while conducting research there.

One of the most exciting additions planned for the library is a new electronic classroom with several computers, a wired lectern, network access and video projector capabilities. "We need this for orientations and instructional programs and for workshops that involve online information resources and the Internet," said SFBR Librarian Danny Jones. "In the future, we will use the electronic classroom for programs on new and emerging information technologies and electronic resources, and we'll be able to offer video conferencing. Right now, there is no place like this on campus."

He pointed out that plans for the library's renovation include back-up space for additional electronic classroom activities in the group-study area.

"While there still will be space for traditional print resources such as books and journals not available electronically, with these improvements, SFBR will have a facility that is on the leading edge of 21st century libraries," said Jones.

Campus addition will enable the work of a new scientific director

To help lead SFBR scientists as they strive to remain on the leading edge of their research fields, SFBR has been fortunate to recruit Dr. Philip LoVerde to serve as the Foundation's new scientific director.

A SUNY Distinguished Professor in the School of Medicine and Biomedical Sciences at the State University of New York, Dr. LoVerde has served in many prestigious appointments on panels sponsored by The Wellcome Trust, UNICEF, the World Bank, the World Health Organization, NIH, and the Bill and Melinda Gates Foundation, among other numerous distinctions.

SFBR faculty and staff are looking forward to the time he can assume his role as the Foundation's chief scientific officer in 2005, but before he can do so, he needs to be able to move his research program to SFBR.

Building a Brighter Future

A new laboratory will accommodate Dr. Philip LoVerde's research program.

Dr. LoVerde's research focuses on schistosomiasis, or bilharzia, a disease caused by parasitic worms. This disease is a major cause of morbidity in 76 countries of the world, where it afflicts more than 200 million people. Although schistosomiasis is not found in the United States, it is a major concern of the military abroad and of those who travel. His research is aimed at elucidating molecular mechanisms of the parasite-host interactions. An understanding of the role schistosome genes and gene products play in these interactions will lead to vaccine candidates, improved diagnostics, and a basis for novel drug design.

Because it is important that Dr. LoVerde continue his valuable research program while serving as the Foundation's scientific director, SFBR trustees recently approved the construction of a new laboratory to accommodate his research program and his scientific staff. At the time of this publication, the 5,500- to 6,000-square-foot facility is still in the planning stages, but its expected completion date is April 2005.

SFBR president reviews success, thanks donors

Reviewing the exhaustive list of campus improvements, SFBR President Dr. Frank Ledford, who plans to retire at the end of 2004, believes he is leaving the Foundation in a good position for the future.

"When I came here 12 years ago, I must admit that there was disappointment over our aging campus, which offered scientists buildings that were constructed back in the 1950s. But together, we developed a modernization plan that was staged over a period of years to renovate or replace nearly all of our laboratories, and we're on schedule with that plan," he said. "Soon, we will have completed more than $50 million worth of work on this campus, and we will have more than completed what we envisioned when we first developed our Campus Modernization Plan back in 1995. I'm very proud of that."

He continued, "As proud as I am of our accomplishments, I appreciate the fact that we have been blessed with a great deal of funding from the National Institutes of Health and from a very supportive group of donors, without whom this success would have been impossible. For example, our first major undertaking, the construction of our $12.5-million virology complex, was funded with $1.3 million in federal dollars. The remaining expenses were all met by donors. Today, as the Phase III and IV renovations are about to begin, we have received $3 million worth of NIH funding, and the remainder of this $10 million project is again being funded by donors. Those are not unusual examples, and I believe they demonstrate the importance of contributed funds to our campus. We are extremely grateful for our many friends and supporters who have helped us get where we are today. Our success story is one they share."

As optimistic as Dr. Ledford is about the positive changes to the SFBR campus,

he cautions that much work still lies ahead. "While our scientists are the ones with the vision to develop the research programs that benefit all our lives, they can't do their work without the proper facilities, and there are rapid changes in new technologies and the demands those technologies place on us. So it is obvious to me that, while our campus is much improved, we really are just beginning a program that will never end. The repair, maintenance and renovation of the physical campus are part of a book with unending chapters."

SFBR Scientific Reports

Major Scientific Achievements

Highlights of progress in 2003

Editorship of a scientific journal comes to SFBR

The Wayne State University Press awarded a contract to locate the editorial office for *Human Biology: The International Journal of Population Biology and Genetics* at SFBR. Dr. Sarah Williams-Blangero, chair of the Genetics Department at SFBR, has taken on the role of editor-in-chief. The two associate editors, Drs. Michael Mahaney and Jeff Williams, also are faculty members in the Department of Genetics. This is another indicator of the high regard shown for our genetics faculty by the genetics research community at the national and international level.

Significant scientific publications

Preventing coronary heart disease by starting in childhood: Dr. Henry C. McGill Jr., senior scientist emeritus in the Department of Physiology and Medicine, wrote an invited editorial for the *Journal of the American Medical Association* titled "Starting Earlier to Prevent Heart Disease." The editorial accompanied two new papers published in the same issue of the journal that showed that the risk factors for adult coronary heart disease measured in childhood – high blood cholesterol, high blood pressure, smoking, and obesity – predicted the severity of atherosclerosis in those same young persons two decades later. These results confirmed a number of reports of results from the Pathobiological Determinants of Atherosclerosis in Youth study previously authored by Dr. McGill and his colleagues. These findings indicate that lifestyle modifications to control these risk factors in childhood are necessary for long-range prevention of coronary heart disease.

Increases in HDL-C recently have been shown to be associated with regression of atherosclerotic plaque size and increases in coronary artery blood flow, indicating a reversal of coronary artery disease.

Promising findings in the hunt for new cancer drugs: Dr. Susan Mooberry, associate scientist in the Department of Physiology and Medicine, identified several new compounds derived from the roots of the bat flower plant, *Tacca chantrieri*, that have anti-tumor activities similar to the cancer drug Taxol™. Taxol™ is used to treat a wide variety of cancers, and new compounds of this nature promise to be effective new cancer drugs, particularly for treating cancers that show resistance to multiple chemotherapeutic agents, including Taxol™. Dr. Mooberry's findings were published in the prominent journal *Cancer Research*.

Unique new model developed for studying human cancers: Dr. Zhiqiang Wang, Dr. John VandeBerg and others authored a paper in *Cancer Research* explaining how scientists at the Southwest Foundation for Biomedical Research have developed a unique new animal model for studying human cancers. The animal is a small

Genetic influence found on "good cholesterol": Dr. Michael Mahaney and other SFBR geneticists involved in the San Antonio Family Heart Study published a paper in the American Heart Association's scientific journal, *Arteriosclerosis, Thrombosis and Vascular Biology*, localizing a gene on chromosome 16 that controls plasma levels of HDL-cholesterol, commonly referred to as the "good cholesterol." Identification of this gene could lead to new drugs that will raise HDL-C.

Major Scientific Achievements

Highlights of progress in 2003

continued

South American opossum known as *Monodelphis domestica*, and it is the first animal with an active immune system that has been able to grow cancer cells and tumors from a human. This development opens the door for a host of promising research opportunities, including the ability to investigate ways to harness a person's own immune system to kill cancer cells, as well as how the immune system and various chemotherapies work together in this same effort.

Learning how to defeat hepatitis viruses: Dr. Robert Lanford, scientist in the Department of Virology, published two new significant findings in hepatitis research. One paper in *Virology* described a new infectious clone of the hepatitis B virus (HBV) that his laboratory discovered in woolly monkeys. Research with cell systems that are infected with this clone could lead to new information in regard to how humans become chronically infected with HBV. The second paper, published in the *Journal of Virology*, described initial observations of agents that could provide antiviral effects against HCV. This research promises to produce information in regard to the mechanisms that can be exploited to produce effective antiviral drugs for hepatitis C, the leading cause of liver failure and liver transplantation in the United States.

New developments in research programs

New studies test therapies for premature infants: Two new studies were initiated in the Neonatal ICU Research Program. One was a comparison of a new ventilation strategy, nasal continuous positive airway pressure (nCPAP), with conventional high-frequency ventilation in premature neonates. Nasal CPAP promises to reduce the amount of permanent lung injury that is associated with the use of high frequency ventilation in neonates. The other new study was a demonstration of impaired brain develop-

ment in baboon neonates exposed to high-dose steroid therapy. This study demonstrates that the premature baboon is a valid model of the impaired brain development that has recently been identified in some human premature infants.

Examining the impact of maternal nutrition on fetal and adult health: Dr. Peter Nathanielsz, an adjunct scientist in SFBR's Depart-ment of Comparative Medicine and director of the Women's Health Research Center at New York University, is a leading researcher in the field of fetal programming, or the fetal origins of adult disease, in which scientists are investigating how one's time in the womb influences his or her health as an adult. Dr. Nathanielsz has moved his entire research program investigating the developmental effects of maternal nutrition on fetal and adult progeny cardiovascular function to SFBR. This promises to develop into a major new research direction at SFBR that will include collaborations and funding for several SFBR research programs.

Expanded role in national biodefense efforts: SFBR continues to play a larger role in efforts to defend the nation against bioterror threats and the risk of emerging infectious diseases. In 2003, the Foundation was named part of a Regional Center of Excellence for Biodefense and Emerging Infectious Diseases for Region VI, one of eight new RCEs established by the National Institutes of Health. The primary research focus of the RCEs is on agents the government has determined to be bioterror threats, often described as "select agents." Examples include anthrax, bubonic plague, Ebola, tularensis, and viral hemorrhagic fevers. The program, however, also addresses emerging infectious diseases such as dengue fever, monkeypox and SARS. As the only institution in the country to house both a biosafety level four (BSL-4), maximum containment laboratory and a National Primate Research Center, SFBR is playing a key role in the RCE for Region VI, which is headed by the University of Texas Medical Branch at Galveston. In total, this RCE unites the efforts of 16 collaborating institutions in five states, all working together to find treatments, cures and improved diagnostics for our country's newest health threats.

Long-standing program on atherosclerosis yields largest grant in SFBR history: The longest-running grant at the Southwest Foundation for Biomedical Research became the largest grant in the Foundation's history when the Baboon Program Project was renewed by the National Heart, Lung and Blood Institute (NHLBI) for $14.7 million over five years. Officially titled "Diet and Genotype in Primate Atherosclerosis," the research program studies baboons to learn how diet and genes interact to determine an individual's risk of atherosclerosis, where fatty substances form deposits of plaque on the inner lining of arterial walls, contributing to heart disease. The program aims to identify particular genes that contribute to atherosclerosis and its risk factors and then to learn how those genes function, eventually leading to the development of individually tailored diets and therapeutic drugs to help prevent and treat the disease.

Department of Comparative Medicine

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

The Department of Comparative Medicine is responsible for the maintenance, health care, and research support of more than 6,000 nonhuman primates and 3,000 other animals at the Southwest Foundation for Biomedical Research.

The department consists of three divisions: Animal Resources, Medicine, and Research Resources. Animal Resources is responsible for the daily maintenance of the 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 an anthropologist who directs 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.

The department 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.

Personnel

The Department of Comparative Medicine was created in 2003 with the merging of related services and personnel from the Department of Laboratory Animal Medicine and the Department of Physiology and Medicine. By coming together under the umbrella of one department, the two groups share a central direction and enjoy a more effective utilization of their combined skills and expertise.

Dr. K.D. Carey, who came to the Foundation in 1976 and had been acting chair of the Department of Physiology and Medicine for the past two years, became the first chairman of the new department. Dr. L.B. Cummins, a veterinarian and primatologist for 30 years, became the associate chair and director of animal resources.

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

man primate colonies at the Foundation. He is recognized for his expertise in the pathology of age-related changes in rodents and nonhuman primates.

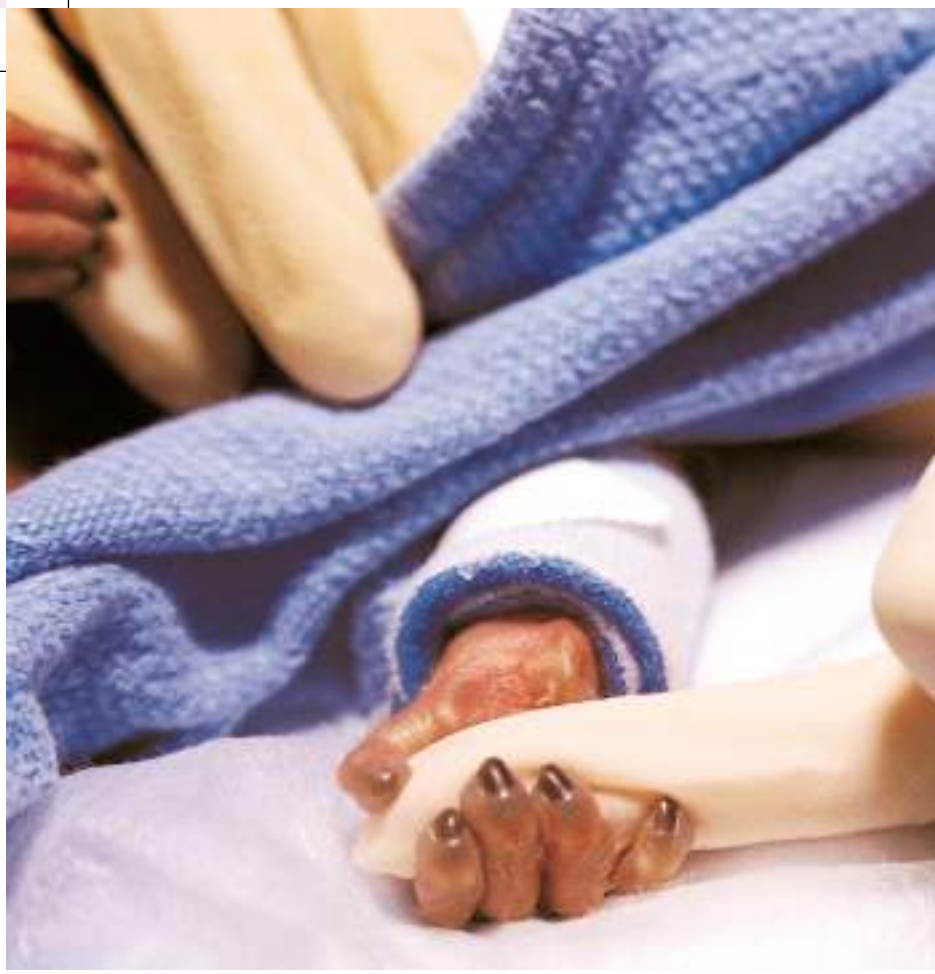
Dr. Kathleen Brasky directs most of the research projects utilizing chimpanzees and has recently become the lead veterinarian for biomedical projects performed in the Foundation's biosafety level four (BSL-4) facility. Dr. Michelle Leland is a skilled surgeon who performs most of the clinical and experimental 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. Stephanie Butler joined the veterinary staff in 2003 after a laboratory animal residency at the University of Tennessee at Memphis. Dr. Linda Brent, who developed and expanded the animal environmental enrichment program at the Foundation, left her full-time position with SFBR to direct Chimp Haven, a chimpanzee retirement facility in Louisiana. With her departure, Dr. Christina Grassi, a recent graduate from the Department of Anthropology at the University of Texas at Austin, joined the department in the fall of 2003 to direct the environmental enhancement program.

Research support

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,

Department of Comparative Medicine



mice, rabbits, South American opossums, and guinea pigs.

The physiological similarities between nonhuman primates and humans make nonhuman primates useful models for a broad range of diseases. Therefore, the department provides research support and collaboration on a large variety of projects with nonhuman primates to study human-health-related disease processes.

Diseases of infancy

The Collaborative Program in BPD (bronchopulmonary dysplasia) brings together senior investigators from around the country to investigate premature lung disease in humans using the premature baboon model. The baboon develops premature lung disease that is very similar to the human disease, allowing researchers to study the disease and test potential new treatment therapies in a controlled environment.

Two exciting developments in this research program occurred in 2003. Investigators spent the summer demonstrating that nasal CPAP (continuous positive airway pressure), a noninvasive mode of ventilation popular in Europe, did not cause the lung damage typically seen in infants treated for extended periods with traditional ventilation therapies, and that it actually improved lung alveolar and vascular development in the premature baboon model. These are encouraging findings in the search for improved treatment methods to rescue and improve the quality of life for infants born prematurely.

In addition, collaborating scientists from SFBR, St. Louis, Boston, and Sidney, Australia demonstrated that the premature baboon 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 effects of the environment on the

developing fetus during pregnancy are called "developmental programming." Extensive studies in several different species show that alterations of the environment during pregnancy have long-term consequences by increasing the offspring's predisposition to conditions such as hypertension, stroke, adult-onset diabetes and perhaps even depression and allergies. The observation that the quality of the environment we experience during pregnancy and during the early neonatal period has implications for life-long health is an area of modern biomedical investigation that is of critical importance to everyone in our society.

A group of adjunct scientists at New York University School of Medicine have been working in collaboration with scientists from SFBR to conduct inter-related studies on developmental programming for the first time in nonhuman primates, looking specifically at the developmental effects of nutrition, hormones, and biorhythms (e.g., sleep cycles and cardiac rhythms).

Another novel program investigates genes that may be associated with variations of maternal-infant interactions and subsequent infant behavior. The project utilizes the large pedigreed baboon colony, baboon behavioral ethograms developed at SFBR, and collaboration with members of the Department of Genetics.

Diseases of adolescence and adulthood

Members of this department have long worked with members of the Department of Genetics in describing baboon models of atherosclerosis, dyslipoproteinemia, and hypertension. More recently, they have collaborated with Dr. Anthony Comuzzie in the Department of Genetics to describe baboon models of obesity and type II diabetes. As the obesity epidemic grows, and with it the incidence of type II diabetes, these animal models are expected to play an increasingly important role in helping scientists find new ways to curb this public health problem.

Baboons also appear to be a natural model for endometriosis, a painful, chronic disease that affects millions of women and girls around the world. Through their own investigation and with consultation from local Air Force gynecologists, SFBR veterinarians have identified a number of naturally occurring cases of endometriosis in the Foundation's baboon colony. With this discovery, researchers now have identified an important animal model for testing new therapies that may eventually be used in human medicine.

Department of Comparative Medicine

Diseases of aging

SFBR veterinarians and investigators in the department have discovered that the aging female baboon experiences many of the same perimenopausal changes as women, including osteoporosis, urogenital changes, an atherogenic lipoprotein profile, and increasing menstrual cycle irregularity. After several years of work, the group has developed a colony of geriatric baboons. With this unique colony, scientists will be able to examine age-related changes in this well-described colony and search for genes associated with those changes.

Complementing the Foundation's work with aged baboons, Dr. Suzette Tardif is developing the marmoset monkey as a model for life-span research. At approximately the size of a rat, marmosets are amongst the smallest of primates. Associated with this small size is a shorter time to mature and a shorter average life span than is typical for larger primates such as baboons, macaques and chimpanzees. This earlier maturation and shorter life span appears to make the marmoset ideally suited for research studies focused on aging and on prenatal or developmental programming. In prenatal programming research, investigators examine how differences in the prenatal environment impact an animal's health in adult years. While this type of lifespan study could take years in other primates, it can be completed in just three to fours years in a marmoset. Dr. Tardif's efforts in this area have recently focused on the effects of maternal nutrition on pregnancy outcome in the marmoset. Marmosets are also potentially important primate models in aging research, given that marmosets are considered aged at eight to nine years old. Therefore, Dr. Tardif has initiated efforts with the University of Texas Health Science Center at San Antonio and the University of Texas at San Antonio to develop a marmoset aging research resource.

Infectious diseases

Veterinarians in the department have a long history of collaborating with scientists in the Department of Virology and Immunology, specifically with research

related to AIDS, hepatitis B and C, and other infectious diseases for which they are trying to develop or test potential new therapies and vaccines. With the nation's current war on terrorism, a new area of research has developed to examine viruses and bacteria that the government has determined to be bioterror threats. Today, the department's veterinary staff plays an important role assisting SFBR virologists as they work with animals to test potential new vaccines and therapies against these agents.

Facilities

Ensuring the humane care and treatment of the Foundation's animal colonies is a primary responsibility of the Department of Comparative Medicine. In that effort, several projects have been funded for facilities construction or renovation aimed at maintaining or improving the animals' quality of life.

- **Primadomes™.** Twelve new Primadomes™ are being constructed to provide spacious indoor-outdoor housing for a number of chimpanzees. The outside facilities are large geodesic domes that incorporate climbing structures, ropes, swings and other features to provide an interesting environment for the chimpanzees.
- **Social cages.** A new set of 20 social cages capable of housing 350 animals was completed this year.
- **Research facility.** Renovation of an animal housing facility has proceeded so that the Foundation can expand its research on infectious diseases. This renovation will provide facilities for testing biologic agents in accord with guidelines of the Center for Disease Control and Prevention.
- **Baboon hospital.** A grant has been funded and architectural plans drawn to renovate facilities currently used as the baboon hospital. In addition to housing the animal clinic, the new facility – when it is completed – will contain laboratories for radiography and sonography.
- **Rhesus monkey housing.** A grant has been funded and architectural plans drawn to construct housing for the Foundation's colony of specific pathogen free (SPF) rhesus monkeys, which provide an important animal model for studying simian immunodeficiency virus (SIV) infection, the simian version of HIV.
- **Shower and locker facility.** A grant has been funded and architectural plans drawn to construct a shower and locker room facility for the department's animal caretakers and veterinary technicians.

Doctoral Staff

(as of December 2003)

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

Associate Chair
Director, Animal Resources
Larry B. Cummins, D.V.M.

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

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 Brent, Ph.D.

Assistant Veterinarian
Stephanie D. Butler, D.V.M., M.S.

Staff Scientists
Massimo Bardi, Ph.D.
Christina Grassi, Ph. D.
Erika Honoré, D.V.M.
Jerilyn K. Pecotte, Ph.D.
Karen S. Rice, Ph.D.

Department of Genetics

Sarah Williams-Blangero, Ph.D.
Chair

The Department of Genetics at the Southwest Foundation for Biomedical Research made remarkable advances during a very exciting year in 2003.

Many of our research programs moved into newly constructed or renovated space, and substantial progress was made on plans to renovate the remaining space in the department by the end of 2005.

A total of $16.2 million was awarded to scientists in the department during 2003 in support of their cutting-edge research on the genetic determinants of complex diseases. These research programs produced a total of 74 publications in the scientific literature during 2003. Funding and publications both increased significantly over the levels achieved last year, indicating that the department continues to be a vital and productive center of genetic research.

Scientists better equipped for genetic discovery

The SBC Genomics Computing Center opened in June 2003. This center houses the world's largest computing cluster dedicated to genetic analysis. With 1,500 processors available to support the intensive computational requirements of genetic studies of common diseases, the resources of the SBC Genomics Computing Center allow departmental scientists to pursue the hunt for genes influencing major health problems at an unprecedented rate of speed. Knowledge of the genetic determinants of susceptibility to complex diseases can be used to effectively target available interventions to those most likely to develop disease. Once the specific genes influencing a disease are identified, this genetic information can be used in drug development efforts to find more effective cures or methods for prevention of disease. Thus, the SBC Genomics Computing Center has a powerful positive

impact on our ability to pursue the Department of Genetics' mission to advance human health through genetic research.

The renovations of the genetics laboratories in the Ewing Halsell Wing and the Robert J. Kleberg Jr. and Helen C. Kleberg Wing of the molecular genetics building also were completed in 2003, providing new homes to five existing research programs and space for a new molecular genetics research initiative. The well-equipped laboratories facilitate state-of-the-art genome scanning efforts that involve characterizing millions of genotypes for studies designed to identify the individual genes influencing susceptibility to heart disease, obesity, diabetes, osteoporosis, psychiatric diseases, behavioral characteristics, and parasitic diseases. In addition, work in these laboratories is generating data on disease-related traits, such as levels of gene expression in fat tissue and cytokine characteristics, for use in genome scans aimed at novel disease processes.

Impact of faculty changes

Changes in the department were not limited to space during 2003. Dr. Bennett Dyke, who in collaboration with Dr. Jean MacCluer pioneered the use of computer methods in genetics in the late 1960s and early 1970s, retired at the end of 2003. Dr. Dyke was one of the first faculty members recruited into the Department of Genetics when it was established in 1982, and the program that he and Dr. MacCluer initiated has flourished into a highly productive statistical genetics effort. The use of parallel processing to increase the speed of genetic analyses was first explored by departmental scientists in 1988. Dr. Dyke played a critical role in the development of these techniques, which are the key to the power of the computing cluster in the SBC Genomics Computing Center.

There were also three additions to the faculty of the department. After completing his postdoctoral fellowship with Dr. John Blangero, Dr. Harald Göring joined

Department of Genetics

the faculty to pursue a research program focused on developing new methodologies for the localization and identification of disease genes. Dr. Shelley Cole, who as a staff scientist directed the department's Genetics Core Laboratory for several years, joined the faculty this year, solidifying the department's strength in the area of cardiovascular disease. The department's strength in research on heart disease also was enhanced by the innovative molecular genetic work conducted by Dr. Laura Cox, which led to her appointment to the faculty in 2003.

Longstanding research on cardiovascular disease forges ahead

Cardiovascular disease, along with its associated risk factors, has traditionally been the primary focus of research in the Department of Genetics. Approximately half of the grant funding awarded to the department during 2003 supported research on cardiovascular disease. Research efforts in this area have included both human and animal studies. The pedigreed baboon colony at SFBR has been used to assess the genetic determinants of response to dietary fat and cholesterol for over 20 years. In 2003, a competitive grant application to the National Institutes of Health for continuing support of the research in baboons resulted in the largest single grant ever awarded to the institution. This $14.7 million five-year grant is directed by Dr. John VandeBerg and involves 10 investigators from the Department of Genetics; it will support the baboon research program through its 25th year.

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 American Indian groups from Arizona, the Dakotas, and Oklahoma. This year a new grant award to Dr. Shelley Cole expanded the human population research to include a study of the genetic components of cardiovascular disease risk factors in families from southwest Ohio.

Expanding research on infectious diseases

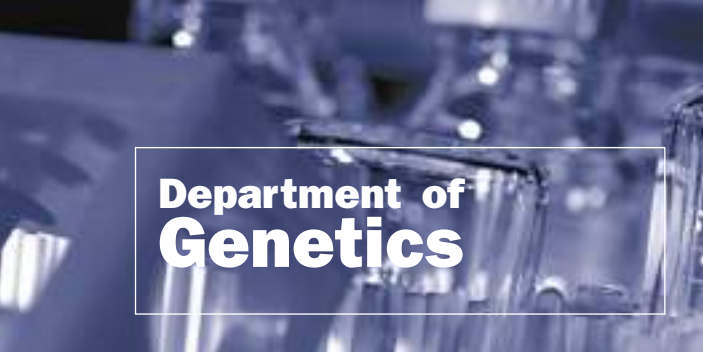
The Infectious Disease Genetics Program started eight years ago with a single grant. It is now the second most highly funded area of research in the department with $2.6 million in grant funding awarded during 2003. This program involves research at several international field sites, including a project on the genetic determinants of drug resistance in malaria parasites based in Thailand, research on the genetic components of susceptibility to Chagas disease based in Brazil, and a project on the genetics of susceptibility to intestinal worm infections based in Nepal.

Pioneering work in the development of animal models

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. In 2003, the *Monodelphis* colony resource again was supported by a generous grant from the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation.

Advances in statistical genetics

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. Approximately $1.7 million in funding was awarded to the department during 2003 in support of these research efforts. Included in this funding was a major contract from AGT Biosciences to Dr. John Blangero to facilitate continued development and use of the computing cluster in the SBC Genomics Computing Center. 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 they could be completed. Over the past five years, a tremendous increase in capabilities has been achieved. With the completion of the SBC Genomics Computing Center this summer, analyses that took two weeks to complete in 1998 now take just three minutes.



Department of Genetics

Burgeoning program on psychiatric disease

Research on the genetic determinants of psychiatric disease and its correlates is one of the newest programs in the department. Research efforts in this area received slightly over $1 million in support during 2003 and focused on the genetic determinants of psychiatric traits in humans and in baboons. This level of funding represents an increase over last year, which is attributable to a new NIH subcontract awarded to Dr. Jeff Rogers. The new program will use the rhesus model for a genetic study of anxious and depressive behavior to be conducted in collaboration with the University of Pittsburgh.

Looking forward

The 2003 year was one of dramatic change for the Department of Genetics. The completion of the SBC Genomics Computing Center and the new laboratories facilitated rapid progress in genetic research that is directly relevant to human health. The $16.2 million of funding support generated by departmental scientists during 2003 exceeded the amount awarded in 2002 by $1.42 million. In addition, departmental scientists documented their advances in 74 publications that appeared during 2003, nine more than appeared in 2002. Through development and refinement of both molecular and statistical techniques, they also expanded the range of tools available to facilitate these research efforts in the future. Given the grant awards and publications already generated for 2004, it is clear that Department of Genetics will experience even greater scientific productivity next year and beyond.

Doctoral Staff

(as of December 2003)

Chair
Sarah Williams-Blangero, Ph.D.

Scientists
John Blangero, Ph.D.
Anthony G. Comuzzie, Ph.D.
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John L. VandeBerg, Ph.D.

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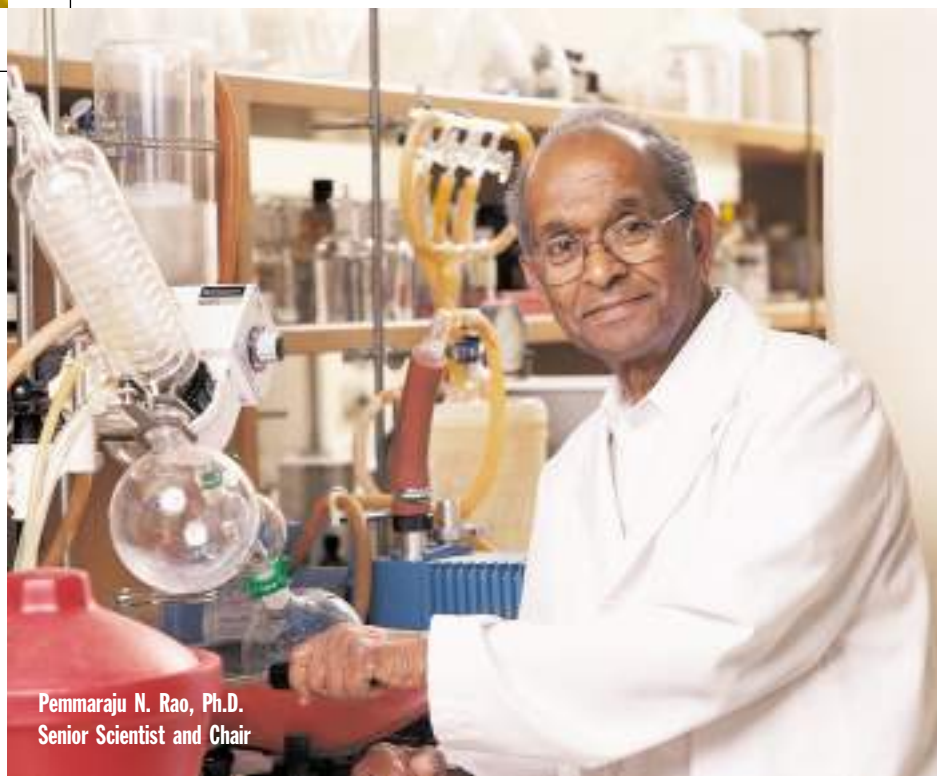
Sobha Puppala, Ph.D.
Cherise J. Rohr, Ph.D.
Qiang Shi, Ph.D.
M. Elizabeth Tejero, Ph.D.
Diane M. Warren, Ph.D.

Department of Organic Chemistry



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

In April 2003, the Department of Organic Chemistry entered into year two of a five-year contract as The Synthetic Chemical Facility for the Contraceptive Development Branch (CDB) of the National Institute of Child Health and Human Development, National Institutes of Health. This marks the 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. Current projects and areas of interest are as follows:

Syntheses of unnatural amino acids

Dr. P.N. Rao and his research staff are synthesizing a variety of unusual amino acids as building blocks for creating analogs of gonadotropin-releasing hormone (GnRH) for use as potential contraceptive agents and treatment of reproductive disorders. Synthetic peptides that both mimic and inhibit GnRH actions have the potential of being nonsteroidal contraceptive agents for both males and females.

Antiprogestins

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

The antiprogestin known as CDB-4124 was conceived and synthesized in Dr. Rao's laboratories. Subsequent biological testing indicated this analog exhibited three times the antiprogesta-

tional 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. The methods developed at SFBR for the synthesis of CDB-4124 are the subject of a pending world patent titled "Process for the preparation of 17∝acetoxy-11∝[4-N,*N*-(dimethylamino)phenyl]-21-methoxy-19-norpregna-4,9-diene-3,20-dione, intermediates useful in the process, and processes for preparing such intermediates."

Male contraceptives

One promising approach to controlling male fertility is through the administration of a single agent that is both antigonadotropic and androgenic. It has been reported that Dimethandrolone has approximately three times the activity of testosterone and a longer duration of action.

The reported synthesis of Dimethandrolone is long and complex. Consequently, Dr. Rao's group has developed an efficient short synthesis of this material that is adaptable to large-scale synthesis. They are currently synthesizing a large quantity of a Dimethandrolone derivative for preclinical studies. The methods developed in Dr. Rao's laboratories for the synthesis of this material are the subject of a pending world patent titled "Preparation of dimethylestrenone alkylcarbonate esters as long-acting androgens."

Novel 2-methoxyestradiol compounds with anticancer activity

2-Methoxyestradiol is a natural metabolite of estradiol devoid of estrogenic or tumor-promoting activity *in vivo*. In 1989 it was discovered that 2-ME2 inhibits the

cellular machinery involved in replicating cancer cells, specifically microtubules, the intracellular target of the well-known. anticancer drug Taxol™. In addition, 2-ME2 has been demonstrated to act as an antiangiogenic agent that prevents the growth of new blood vessels required to nourish tumors.

Upon learning these findings, the Department of Organic Chemistry initiated a program to investigate the potential anticancer application of prior and newly synthesized 2-ME derivatives. In collaboration with Dr. Susan Mooberry of the Department of Physiology and Medicine, these compounds were tested for antiproliferative activity against breast and ovarian cancer cells. Three of the analogs were found to have promising activity.

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 by Dr. Rao for the synthesis of these analogs and their biological effects are the subject of a pending patent titled "Novel 2-alkoxyestradiol analogs with antimitotic activity."

In July of 2003, the Department of Organic Chemistry entered into a six-month sponsored research agreement with Entremed Inc. of Rockville Maryland titled "Synthesis of new 2-methoxyestradiol analogs." Under this contract, researchers in the department have synthesized 10 new 2-ME2 analogs for biological evaluation by Entremed. Preliminary results from *in vitro* testing indicate one new compound with promising results. Entremed has extended its support for an additional year, and the department is currently developing new 2ME-2 analogs under this research agreement.

Doctoral Staff
(as of December 2003)

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

Department of Physiology and Medicine

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

Research in the Department of Physiology and Medicine focuses on two major areas of biomedical research: cardiovascular diseases and cancer drug discovery. In these research efforts, departmental faculty collaborate extensively with investigators from other departments at SFBR as well as at other institutions throughout the United States and around the world. Results of their investigations in 2003 have led to several new advances in biomedical research.

Cancer drug discovery

Dr. Susan Mooberry's laboratory continues the search for new drugs that may be useful in the treatment of cancer. In the past year, several different classes of natural and synthetic compounds were identified and evaluated for activities that may predict anticancer effects. The basic approach used in this research is to examine the effects of these compounds on cellular structures called microtubules. Microtubules are used by cells to guide genetic material into the two new daughter cells during the cell-division process. Disruption of microtubule function inhibits cell division and signals cancer cells to initiate apoptosis, or cellular death.

Taxol™, a drug used in the treatment of many different types of cancer, was first identified from the bark of the Pacific yew tree. Unlike many other anticancer drugs that destabilize cellular microtubules, Taxol™ acts as a microtubule stabilizer. Microtubules need to be dynamic for successful cell division, so when microtubules are stabilized, the cell recognizes that something is inherently wrong and initiates its own destruction. This makes Taxol™ an important drug for cancer treatment, and the search continues for new drugs that share the same mechanism of action, particularly for the treatment of Taxol™-resistant tumors.

In 2003, Dr. Mooberry and her research team identified the first new class of microtubule stabilizers derived from a plant since Taxol™. These compounds, called taccalonolides, were isolated from the tropical bat flower plant. Although

chemically unrelated to Taxol™, the taccalonolides cause an increased density of cellular microtubules, interrupting normal cell division and leading to the initiation of a cellular suicide program in cancer cells. Preclinical testing of the taccalonolides in animal models of cancer continues with the goal of determining whether they have potential to treat cancer.

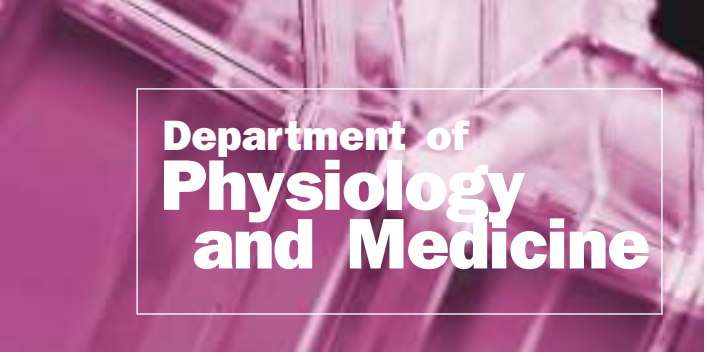
Laulimalide is another Taxol™-like microtubule stabilizer that was identified in Dr. Mooberry's screening program. Unlike the taccalonolides, it was originally derived from a marine sponge. Laulimalide has promising activities against cancer cells, but it has chemical characteristics that cause it to be unstable. In collaboration with Dr. Paul Wender and his group at Stanford University, Dr. Mooberry's laboratory evaluated new synthetic laulimalide analogs that were designed to have superior chemical stability. Two analogs with potent antiproliferative activities were identified.

The marine environment is the source of many new cancer drugs, and in collaboration with Dr. Richard Moore's group at the University of Hawaii, Dr. Mooberry's group identified a new dolostatin 10 analog called symplostatin 1 from a marine cyanobacterium. Symplostatin 1 causes the loss of cellular microtubules, disruption of mitotic spindles, and abnormal mitosis, leading to cellular suicide. In mouse models used to predict effects in humans, symplostatin 1 had antitumor activities against a mammary tumor and a colon tumor.

Halting tumor growth by preventing the generation of a new blood supply, a process called angiogenesis, holds great promise for controlling cancer. 2-Methoxyestradiol is a natural metabolite of estrogen that is currently in early-phase clinical trials. In collaboration with Dr. P.N. Rao and his team in the SFBR Department of Chemistry, Dr. Mooberry's lab tested new analogs of 2-methoxyestradiol for superior activities. Two of the compounds had better antitumor effects in a mouse breast cancer model. Studies with these two new derivatives are ongoing to determine whether they have advantages over the parent compound.

Atherosclerosis research

Dr. Rampratrap Kushwaha's laboratory focuses on the metabolic mechanisms that regulate plasma lipoproteins. Recently this program



Department of Physiology and Medicine

Doctoral Staff
(as of December 2003)

Acting Chair
Robert E. Shade, Ph.D.

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

Scientist
Rampratap S. Kushwaha, Ph.D.

Associate Scientist
Susan Mooberry, Ph.D.

has been using the laboratory opossum, *Monodelphis domestica*, as an animal model of diet-induced hyperlipidemia. Selective breeding of this colony maintained at the Foundation by Dr. John VandeBerg's laboratory has produced strains that have either a high or low response in plasma cholesterol levels to high-cholesterol and high-fat dietary challenge. Dr. Kushwaha's program is investigating the mechanisms that form the genetic basis for these responses with the objective of finding biochemical markers that will predict an individual's risk for diet-induced atherosclerosis.

Genetic analysis suggested that a major gene locus for very low-density lipoproteins (VLDL) and LDL cholesterol explains 80 percent of the control of LDL cholesterol by dietary challenge in opossums. Studies were conducted to determine whether the differences in plasma cholesterol responses to diet between high- and low-responding opossums are due to dietary cholesterol, fat or both. Twenty-four opossums from the high-responding line and 26 opossums from the low-responding line were selected for these studies. Initially, all the animals were maintained on a low-cholesterol, low-fat basal diet. Plasma cholesterol concentrations increased significantly in high-responding animals on diets containing elevated levels of cholesterol alone or cholesterol and fat, but not fat alone. Similarly, plasma cholesterol concentration increased significantly in low-responding animals on diets containing elevated cholesterol levels, but the extent of increase was much less These results suggest that the major gene for dietary response previously detected by genetic analysis in laboratory opossums affects the response to dietary cholesterol but not fat. However, increased fat along with increased cholesterol amplifies the dietary response in opossums.

Salt and Water Metabolism in Blood Pressure Regulation

Dr. Robert Shade's research investigates the role of salt and water metabolism on blood pressure regulation. Much of this research is concerned with renal mechanisms that regulate body salt- and water-composition, which in turn have an effect on blood pressure. However, salt- and water-intake behavior also contribute to the determination of water- and electrolyte-body composition. Studies involving human subjects and using brain imaging techniques such as positron emission tomography (PET) and functional magnetic resonance (fMR) were used to identify regions of the brain that became activated when subjects were induced to become thirsty by infusion of a salt solution. The PET studies were conducted in collaboration with Dr. Peter Fox at the University of Texas Health Science Center at San Antonio Research Imaging Center, and the fMR imaging studies were conducted in collaboration with Drs. Gary Egan, John Blair-West and Derek Denton at the University of Melbourne and the Howard Florey Institute of Experimental Physiology and Medicine. These studies identified areas in the brain that were previously shown in thirst studies with animals to be stimulated by saline infusion. The studies in human subjects also identified several additional areas in the brain that are known to contribute to conscious thought. These latter areas were proposed to be the key portions of the brain that promote water-drinking behavior during dehydration. Future studies will use similar techniques to investigate the decrease in thirst mechanisms that is known to occur in aging humans.

Department of Virology and Immunology

Jean L. Patterson, Ph.D.
Chair

To defeat viruses that cause AIDS, hepatitis, herpes, hemorrhagic fevers, and a host of other devastating diseases, scientists in the Department of Virology and Immunology are studying how these viruses replicate and propagate, how the human immune system recognizes them, and how to stimulate the immune system to clear viral infections.

To assist in these efforts, SFBR virologists have access to some of the best-equipped laboratories in the world, including the nation's only privately owned biosafety level four (BSL-4) maximum containment laboratory. Also extremely valuable to their research efforts are the nonhuman primates 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.

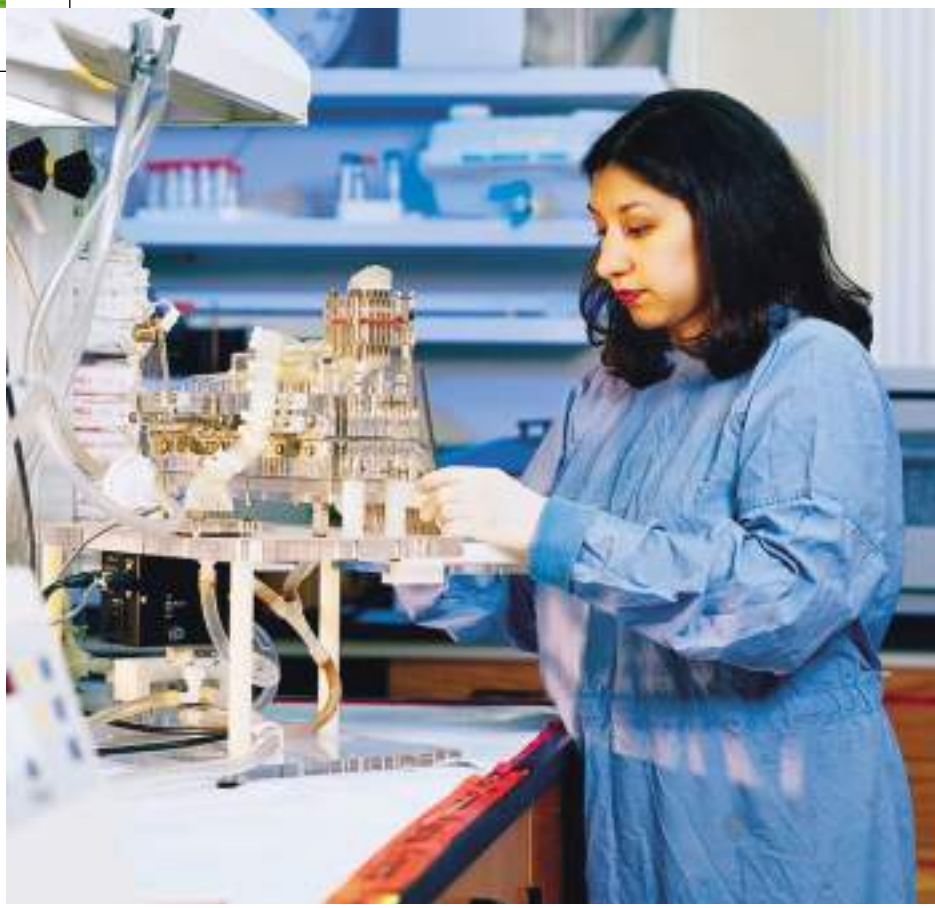
Retroviruses and AIDS

It has been two decades since the discovery of HIV as the causative agent of AIDS. During that period, 23 million people have died of AIDS and an estimated 40 million have become infected worldwide. Although anti-retroviral drugs have lengthened and improved the quality of life for people with HIV, only a small percentage of HIV-infected individuals who live in developing countries have access to these medicines. Therefore, development of an HIV vaccine remains critical.

In this effort, Dr. Luis Giavedoni studies simian immunodeficiency virus (SIV) in rhesus macaques, which have proven to be an invaluable animal model for testing candidate vaccines before human trials. To date, the most effective candidate vaccines in this animal model have been live-attenuated vaccines, which consist of viruses that have been weakened by genetic manipulation to the point that they are still infectious but do not induce disease. These vaccines are not yet appropriate for human use, though, because the vaccine virus has been shown to incorporate itself into the animal's genome and cause complications years after vaccination.

Dr. Giavedoni's laboratory is trying to identify the type of protective immune responses induced by these live-attenuated

Department of Virology and Immunology



vaccines. Once those "correlates of protection" are identified, safer vaccines can be pursued that induce the same type of immune response without the complications. During the last year, his research results indicated that some cells of the immune system that recognize and kill virus-infected cells (cytotoxic lymphocytes) were activated after challenge with SIV and mediated protection. This indicates that induction of these cytotoxic cells must be a critical outcome of any potential vaccine against HIV.

Dr. Krishna Murthy also is researching potential AIDS vaccines through studies with chimpanzees, the only animal besides humans susceptible to HIV infection. Unlike humans, however, chimpanzees show a natural resistance that keeps them from developing AIDS. In collaboration with Dr. Guroff of the National Institutes of Health, Dr. Murthy is testing a novel vaccine strategy utilizing adenovirus vectors expressing the *nef* gene of HIV. This *nef* gene is essential for pathogenesis, or the development of disease, so the induction of immune responses to the gene product is anticipated to prevent infection and pathogenesis following exposure to the virus.

Dr. Jonathan Allan is taking a different approach to AIDS research, trying 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 African monkeys can pose a serious health risk to humans. Based on Dr. Allan's studies thus far, it appears that African monkeys naturally curb immunologic damage both by limiting the number of infected cells and by diminishing host immune response to infection. In collaboration with Dr. Luis Giavedoni, his laboratory is detailing differences in both viral and host response to infection in African monkeys that contribute to a lack of disease with the hope that they can identify key features that will translate into therapies for HIV-infected humans.

Additionally, Dr. Allan is studying samples from humans exposed to monkeys in Asia for possible transmission of simian retroviruses including AIDS and simian foamy viruses. These surveillance efforts are an important part of a quest to detect the introduction and emergence of new human disease.

Dr. Paul Zhou is following an innovative route to design new and improved therapies for HIV and AIDS. Despite the dramatic success of current anti-retroviral drugs in suppressing HIV-1 in infected individuals, they cannot eradicate the virus, they require life-long therapy, and they have many serious problems: toxicity, occurrence of drug-resistant strains, and poor adherence by patients because of the difficult regimens required. Thus, the long-term clinical benefit of the current drug therapy is likely to be limited. This disturbing reality points out the urgent need to develop new drugs and new modes of therapy. The research in Paul Zhou's laboratory focuses on developing genetic therapies against HIV. Compared with conventional drug therapy, the use of genetic therapies has two distinct advantages. First, genetic therapies are directed against broad targets in the HIV life cycle. Most of these targets are distinct from those inhibited by antiviral drugs and thus minimize the potential for the development of cross-resistant viruses. Second, genetic therapies have potential for life-long efficacy following a successful treatment.

During the past year Dr. Zhou's laboratory has made important progress in the following three areas of research. First, he and his co-workers developed an HIV-1-based gene delivery system that efficiently introduces foreign genes into both human and nonhuman primate cells. Currently, they are using this system to deliver anti-HIV-1 genes into both human and nonhuman primate cells to study their anti-HIV activities. Second, he and his co-workers unexpectedly discovered a new modality of inhibiting HIV-1 with antibody molecules. His group demonstrated that a bona fide non-neutralizing human anti-HIV-1 antibody, when produced as a soluble protein, does not neutralize HIV-1 entry. However, when expressed on the surface of HIV-1 susceptible cells, it blocks HIV-1 replication and cell-cell fusion. Thus, on the cell surface this antibody acts as a neutralizing antibody. This finding may not only shed some new light on how HIV-1 enters target cells, but also lead to a new therapeutic strategy to fight HIV-1. Third, he and his co-workers constructed several novel receptor molecules and demonstrated that one of these receptors is extremely potent against diverse viral strains from several HIV-1 subtypes.

Hepatitis C

Hepatitis C virus (HCV) infects 2 to 3 percent of the world's population, with an estimated 170 million chronic carriers. In the United States, an estimated 4 percent of the adult population is chronically infected. The disease has been described as the silent epidemic for two reasons: most individuals are unaware of their infection, and the infection causes a gradual increase in liver disease for several decades before patients become aware of the symptoms. Approximately 20 percent of chronic infections will progress to

cirrhosis, end-state liver disease or liver cancer, making it the leading cause of liver transplants in the United States and Europe.

In 2003, several aspects of Dr. Robert Lanford's research program on HCV merged for unprecedented progress. His laboratory demonstrated for the first time the feasibility of producing a vaccine that would be protective against all strains or genotypes of HCV. HCV is a highly divergent virus with six different genotypes that markedly differ from each. There was considerable pessimism in the research community regarding the potential to produce a vaccine that would protect against all the divergent stains. However, Dr. Lanford's studies negate this concern, since chimpanzees that have cleared infection with one strain of the virus show protective immunity in subsequent challenges with other, highly divergent HCV strains.

In addition to a vaccine, improved therapies are desperately needed to treat people already infected with hepatitis C. Dr. Lanford has spent the past decade perfecting the chimpanzee model of HCV infection, since the chimpanzee is the only animal besides man susceptible to this infection. Unlike humans, however, the chimpanzee does not develop liver disease from HCV, and 70 percent of chim-

panzees clear the infection altogether, as opposed to 30 percent of humans. Today, Dr. Lanford's laboratory works with many top pharmaceutical and biotech companies to examine new antivirals in the chimpanzee model of HCV infection, and results are very encouraging.

In addition, he is trying to gain a better understanding of the events occurring in the liver during HCV infection so that this information can be used in the development of novel therapies. Working with small liver biopsy samples and a technique called microarray analysis, his group has been able to determine all of the changes that occur in gene expression during HCV infection. This work is critical to truly understanding the disease process.

The chimpanzee model by itself has some limitations that prevent certain types of experiments. For this reason, Dr. Lanford's team developed the GBV-B virus model in the tamarin monkey. GBV-B virus is very closely related to HCV and causes hepatitis similar to HCV. Thus, this model can be used as a surrogate to better advance our understanding of HCV.

Although HCV cannot be grown in the laboratory, Dr. Lanford's group has developed a tissue culture system for GBV-B using primary tamarin hepatocytes. This year they extended these studies to demonstrate that the marmoset can be used in place of tamarins for GBV-B studies. This is very important since very few tamarins are bred in primate centers, while the Foundation has a large colony of marmosets.

Investigating HCV's "infectious window period"

Screening blood donors for hepatitis C has significantly reduced the transmission of HCV infection through blood transfusions in the United States. However, there is still a risk of one out 250,000 units of blood product that can transmit infection because the donor is seronegative and the viral load is below the sensitivity range of the NAT assay utilized for the diagnosis of HCV infection. Therefore, Dr. Krishna Murthy is conducting a study to determine HCV's "infectious window period." Results to date suggest that it is as short as seven to 10 days, and further investigation is underway to confirm this finding. Outcome from this study is likely to influence the selection of blood donors and will provide more stringent guidelines for preventing transfusion-associated transmission of HCV. This study is being conducted in collaboration with Dr. Harvey Alter of NIH and Dr. Mike Busch of Pacific Blood Center.

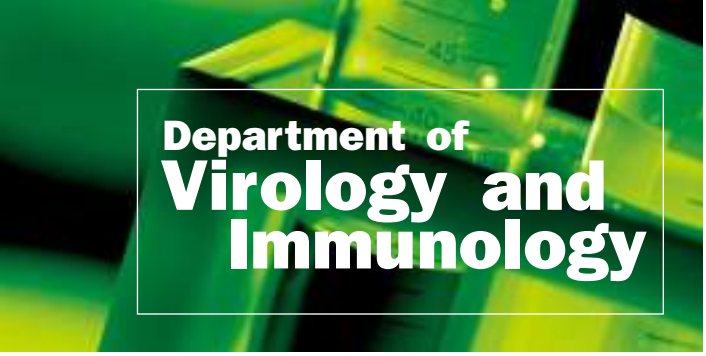
Herpes simplex virus

Dr. David Martin's laboratory focuses on the development of new model systems that will define critical aspects of herpes simplexvirus biology and allow for the design of better strategies to interfere with virus replication. In addition, these studies will assist in the continued development of gene and cancer therapy strategies that use modified herpesviruses as a delivery system.

The primary model system currently under development involves herpesvirus papio 2 (HVP2) infection of baboons. Because HVP2 is closely related to human herpesviruses, this model will provide a powerful surrogate system to study virus biology in the context of a nonhuman primate host.

Emerging and exotic viruses

Little is known about the pathogenesis of dengue fever and dengue hemorrhagic fever, which are caused by mosquito-borne viruses. There are no vaccines or treatments for these diseases, which already have been identified along the U.S.-Mexico border. In an attempt to better understand these diseases so that vaccines and treatments can be created, Dr. Rebeca Rico-Hesse's laboratory has developed two new assay systems (human blood cells and mosquitoes) in which to measure dengue virus virulence in lieu of an animal model of



Department of Virology and Immunology

disease. Pilot studies are ongoing to determine if severely immunosupressed mice that have been engrafted with human blood cells will serve as a model in which to study the immunology of dengue infection.

In collaboration with the University of Maryland, Dr. Jean Patterson's lab continues to work on a vaccine to Lassa fever, an often fatal infectious disease that infects several hundred thousand people a year in West Africa. The vaccine under investigation is a reassortant virus between Mopeia, a non-virulent old world Arenavirus, and Lassa. Early studies at SFBR show it to be effective against a Lassa fever virus challenge.

Dr. Patterson's research team also continues to play a key role in national biodefense efforts. The group teamed up with the University of Texas at Austin to investigate a high-affinity antibody designed to clear the body of the deadly toxin produced by anthrax, which is what kills individuals with late-stage anthrax infection. That antitoxin proved safe and effective in laboratory rats in 2002, and work was done in 2003 to continue refining and testing the antibody. The group plans to take the anthrax antidote into nonhuman primate trials in 2004. If those trials also show it to be safe and effective, the government is likely to stockpile it for use in the event of another anthrax outbreak.

In another ongoing collaboration with the University of Texas Health Science Center at San Antonio, Dr. Patterson and her staff continue to work on an oral vaccine against multiple biological weapons, including anthrax and rabbit fever (*F. tularensis*).

With access to the nation's only privately owned BSL-4, maximum containment laboratory, this SFBR research team also provides resources and assistance to other investigators who need high containment laboratories to test their products related to biodefense and emerging diseases. The Foundation assumed a larger role in this effort – and more funding to support it – with its appointment in 2003 as part of a Regional Center of Excellence for Biodefense and Emerging Infectious Diseases for Region VI. This RCE, headed by the University of Texas Medical Branch at Galveston, unites the efforts of 16 institutions in five states as they try to find treatments, cures and improved diagnostics for our country's newest health threats.

Doctoral Staff

(as of December 2003)

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
David W. Martin, Ph.D.

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F. Alex Hamill, Ph.D.
Vida L. Hodara, Ph.D.

Postdoctoral Scientists
Philip Armstrong, Sc.D.
Dennis Bente, D.V.M.
Ricardo Carrión, Ph.D.
Raymond G. Cologna, Ph.D.
Seung Jae Lee, Ph.D.

Southwest National Primate Research Center

John L. VandeBerg, Ph.D.
Director

The Southwest National Primate Research Center (SNPRC) was established on June 1, 1999, as the first new national primate center funded by the National Institutes of Health (NIH) in over 35 years. In 2003, at the close of our first five-year funding cycle, we take pride in our accomplishments to date and are excited about our potential for the future.

For historical reasons, our center is funded at a far lower level than the other seven NPRCs, which were established in the early 1960s. However, despite the limited financial support that we receive from NIH, we have made giant strides in developing the SNPRC as a national resource.

We have increased our nonhuman primate census by an astounding 30 percent to more than 4,500, not including a significant number of cynomologus macaques supported by a contract from private industry. This places SNPRC second among all the national primate centers in the number of primates that we maintain as a national resource and make available to biomedical researchers throughout the country.

We also rank second among the primate centers in the amount of funding that NIH has awarded during the last five years in grants that support construction and renovation. These grants are highly competitive, and the SNPRC has won most of them in open competition with hundreds of first-rate universities and independent research institutes, in addition to the other national primate research centers. Today, five years after the inception of the base grant, the primate facilities have been transformed into modern structures that are comfortable for the animals and efficiently designed for the caretakers.

Projects completed during the first five years of the SNPRC

- **Chimpanzee Primadomes™:** These units, which provide indoor and outdoor chimpanzee housing in an environmentally rich setting, are nearing completion. Built with NIH funding, they will provide long-term housing for animals not participating in studies.

Southwest National Primate Research Center

- **Improvement of chimpanzee ABSL-2 housing:** Outdoor cages were added to 12 units with NIH funding and matching funds from the SFBR. With these additions, chimpanzees participating in studies will have access to spacious outdoor enclosures.
- **B-, C-, and D-cages:** Our baboon caging complex was given a makeover with NIH funding and matching funds from SFBR.
- **F-cages:** This new wing of caging houses about 300 baboons and was completed in October 2003. Funding was provided by NIH with matching funds from SFBR.
- **Sheltered group housing** was constructed using SNPRC funds to provide expanded baboon housing and housing for our growing macaque population.
- **Generators:** Back-up power units have been installed to support animal facilities in the event of a power outage. This project was funded by NIH grants.
- **Building 23/24:** Quarantine facilities have been upgraded to accommodate the housing of animals involved in research that requires biosafety level 2 and 3 conditions. The work is ongoing under support from NIH and matching funds form SFBR.
- **ABSL-2 and ABSL-3 modular buildings:** New modular buildings are being installed to accommodate small primates involved in research projects with level 2 and level 3 infectious agents. The site preparation and buildings will be

paid for with a combination of SNPRC base grant funds and SFBR funds.

Projects in progress

- **SPF Rhesus Building:** NIH has approved plans and we are now reviewing bids for construction of this project.
- **Shower and Locker Room:** New facilities for the animal care staff will be built in the coming year with NIH and SFBR funds.

Benefits of new and upgraded facilities for scientific research

The improvement and expansion of animal housing facilities will support new and varied investigations, further strengthening the SNPRC's role as a national resource for primate researchers. ABSL-2 and ABSL-3 animal housing provides needed space for research into emerging bioterror threats, as well as *in vivo* testing for vaccines and therapies to treat infectious diseases such as West Nile virus, dengue hemorrhagic fever and SARS. Likewise, the fight against AIDS will be aided by the new facility for a growing colony of rhesus macaques, which are needed to ease a critical shortage faced by AIDS researchers throughout the United States.

SNPRC's growth has far-reaching impact

The rapid growth in SNPRC primate colonies and facilities has had a major impact on our capability to support world-class research programs directed by investigators located at SFBR and at other institutions around the country. During its first five years, our center has supported 267 investigators located at different institutions in 27 states. Some of these research programs are aimed at better understanding – and ultimately developing new preventions and treatments for – diseases

such as atherosclerosis, hypertension, obesity, diabetes, hepatitis C, and HIV/AIDS. Others are focused on understanding phenomena that affect health. Examples include *in utero* environmental conditions that have effects throughout life and the identification of genes responsible for variation in neurotransmitter availability and behavior.

The first annual report of the SNPRC documented $13,564,491 in NIH funding to investigators who depended on the SNPRC for primates or other resources; the fifth one documented $44,659,158. This three-fold growth is testimony to the success of our center in fulfilling its mission as a national resource.

We are now poised to capitalize on the momentum that we have achieved. The next five years are certain to be even more exciting and productive than the first.

Doctoral Staff

(as of December 2003)

Core Scientists

John L. VandeBerg, Ph.D., Director
Department of Genetics

Suzette D. Tardif, Ph.D., Associate Director
Department of Comparative 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

Michael C. Mahaney, Ph.D.
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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 and 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 and Scientific Computing

Postdoctoral Scientist

Darlene A. Smucny, Ph.D.

New grants and contracts awarded in 2003

FEDERAL RESEARCH GRANTS FROM THE NATIONAL INSTITUTES OF HEALTH

	Length of Grant	Total Amount to SFBR
Diet and Genotype in Primate Atherosclerosis Dr. John VandeBerg, principal investigator	5 years	$ 14,685,681
Genetic Epidemiology of CVD Risk Factors Dr. Shelley Cole, principal investigator	4 years	$ 1,723,568
Regional VI Center for Biodefense and Emerging Infections: Nonhuman Primate Core Dr. David Walker, UTMB-Galveston, principal investigator; Dr. Suzette Tardif, SFBR, project leader	5 years	$ 1,365,475
Genetics of Anxious and Depressive Behavior Dr. Judy Cameron, University of Pittsburgh, principal investigator; Dr. Jeffrey Rogers, SFBR, project leader	5 years	$ 869,601
Genetic Regulation of Adiposity and Associated CVD Risks Dr. Brad Towne, Wright State University, principal investigator; Dr. John Blangero, SFBR, project leader	5 years	$ 749,328
Anthrax Antidotes in Animals Dr. Brent Iverson, University of Texas at Austin, principal investigator; Dr. Jean Patterson, SFBR, project leader	3 years	$ 536,282
Regional VI Center for Biodefense and Emerging Infections: BSL4 Core Dr. David Walker, UTMB-Galveston, principal investigator; Dr. Jean Patterson, project leader	5 years	$ 512,687
Immunogenicity of HSV Amplicons in Rhesus Macaques Dr. David Martin, principal investigator	2 years	$ 503,250
Inhibition of HIV by Novel Chimeric Receptors Dr. Paul Zhou, principal investigator	2 years	$ 501,135

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	Length of Grant	Total Amount to SFBR
LHRH Synthetic Peptide Vaccine for Prostate Cancer Dr. Connie Finstad, United Biomedical Inc., principal investigator; Dr. Krishna Murthy, SFBR, project leader	5 months	$ 220,583
Production of Time-Mated Baboons Dr. Peter Nathanielsz, NYU School of Medicine, principal investigator; Dr. Larry B. Cummins, SFBR, project leader	1 year	$ 206,230
Xiphophorus Gene Map Saturating of Identification of Genes Regulating Tumor Development Dr. Ronald Walter, Southwest Texas State University, principal investigator; Dr. Paul Samollow, SFBR, project leader	1 year	$ 198,531
An Oral Vaccine Against Multiple Biowarfare Agents Dr. Karl Klose, UT Health Science Center at San Antonio, principal investigator; Dr. Jean Patterson, SFBR, project leader	2 years	$ 186,240
Regional VI Center for Biodefense and Emerging Infections: Antifiloviral Chemical Screening and Drug Discovery Dr. David Walker, UTMB-Galveston, principal investigator; Dr. F. Alex Hamill, SFBR, project leader	2 years	$ 195,564
Multiplex MHC Typing of Rhesus Macaques Dr. Luis Giavedoni, principal investigator	2 years	$ 169,000
Mopeia/Lassa Virus Reassortants as Lassa Fever Vaccines Dr. Igor Lukashevich, University of Maryland Biotech.Institute, principal investigator; Dr. Jean Patterson, SFBR, project leader	1 year	$ 161,825
Development of Hepatitis C Virus-Like Particles as a Candidate HCV Vaccine Dr. Krishna Murthy, principal investigator	1 year	$ 148,148
Total Federal Research Grants		**$22,933,128**

COMMERCIAL RESEARCH CONTRACTS

Major Research Contracts ($100,000 or more)

Department of Comparative Medicine (7)	$ 2,079,303
Department of Genetics (3)	$ 699,612
Miscellaneous (under $100,000 each)	$ 950,878
Total Commercial Contracts	**$3,729,793**

RESEARCH GRANTS FROM PHILANTHROPIC DONORS

	Length of Grant	Total Amount to SFBR
USAA *Scientific Recruiting* For the recruitment of Dr. Andrew Hayhurst	3 years	$ 500,000
Robert J. Kleberg, Jr. and Helen C. Kleberg Foundation *Monodelphis Research Program* Dr. John VandeBerg, principal investigator	1 year	$ 339,000
Minnie Stevens Piper Foundation *Support for NICU* Dr. K. Dee Carey, principal investigator	1 year	$ 105,000
Kronkosky Charitable Foundation *Cellular Action of Glucose Regulatin in a Non-Human Primate Model of Type 2 Diabetes* Dr. Anthony Comuzzie, principal investigator	1 year	$ 50,000
Kronkosky Charitable Foundation *Search for Genes Influencing Type 2 Diabetes-Related Traits on Chromosome 9 in Mexican Americans* Dr. Ravindranath Duggirala, principal investigator	1 year	$ 50,000
Myra Stafford Pryor Charitable Trust *Equipment for an NICU Patient Bed* Dr. Jacqueline Coalson, principal investigator	3 years	$ 50,000
Morrison Trust *Early Detection of Infection of Premature Infants* Dr. Jacqueline Coalson, principal investigator	1 year	$ 35,734
Ray Ellison Charitable Fund of the San Antonio Area Foundation *Neurological Morbidity in Extremely Low Birth Weight Babies* Dr. Jacqueline Coalson, principal investigator	1 year	$ 30,000
Joe and Jessie Crump-Crippled Children's Foundation *Efficacy of nCPAP in a Baboon Model of Neonatal Chronic Lung Disease* Dr. Jacqueline Coalson, principal investigator	1 year	$ 30,000
San Antonio Area Foundation from the Semp Russ Foundation *Cell-Mediated Immune Response to RSV in Baboons* Dr. Krishna Murthy, principal investigator	1 year	$ 30,000
Southwest Foundation Forum *Genetics of Resistance to Simplexvirus Infection in Baboons* Dr. David Martin, principal investigator	1 year	$ 25,000
Southwest Foundation Forum *Renal Cell Gene Expression Profiling to Identify a Hypertension-Related Gene* Dr. Laura Cox, principal investigator	1 year	$ 24,910

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	Length of Grant	Total Amount to SFBR
Southwest Foundation Forum *Immunogenetics of the Laboratory Opossum* Dr. Nicolas Gouin, principal investigator	1 year	$ 24,823
Edouard Foundation *New BSL-4 Containment Suits* Dr. Jean Patterson, principal investigator	2 years	$ 24,000
San Antonio Area Foundation from the Semp Russ Foundation *Role of DC-SIGN in HIV Infection* Dr. Jason Kimata, principal investigator	1 year	$ 24,000
Shelby Rae Tengg Foundation *Anticancer Drug Development* Dr. Susan Mooberry, principal investigator	1 year	$ 20,000
San Antonio Area Foundation from the Semp Russ Foundation *Genetic Analysis of the Endocrine Function of Adipose Tissue in a Slim Population* Dr. Harald Göring, principal investigator	1 year	$ 18,915
Peter and Beth Dahlberg *Cardiovascular Research* Dr. Henry C. McGill Jr., principal investigator	1 year	$ 3,423
Total Philanthropic Grants		**$1,384,805**

FEDERAL CONSTRUCTION GRANTS FROM THE NIH

Improvement of Primate Clinical Care Facilities Dr. John VandeBerg, principal investigator	1 year	$ 462,272
Extramural Research Facilities Construction Dr. Robert Shade, principal investigator	2 years	$ 3,096,536
Improvement of Centralized Cage Washing Facilities Dr. John VandeBerg, principal investigator	1 year	$ 221,415
Total Federal Construction Grants		**$ 3,780,223**
TOTAL OF NEW GRANTS AND CONTRACTS AWARDED DURING 2003		**$31,827,949**

SFBR 2003 Scientific Publications

Afshar, S., Gibson, L. L., Yuhanna, I. S., Sherman, T. S., Kerecman, J. D., Grubb, P. H., Yoder, B. A., McCurnin, D. C., & Shaul, P. W. (2003). Pulmonary NO synthase expression is attenuated in a fetal baboon model of chronic lung disease. *American Journal of Physiology. Lung Cellular and Molecular Physiology, 284,* L749-L758.

Allan, J. S. (2003). Understanding xenotransplantation risks from nonhuman primate retroviruses. *Current Topics in Microbiology and Immunology, 278,* 101-123.

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Baerlocher, G. M., Mak, J., Roth, A., Rice, K. S., & Lansdorp, P. M. (2003). Telomere shortening in leukocyte subpopulations from baboons. *Journal of Leukocyte Biology, 73,* 289-296.

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Bastarrachea, R. A., Tejero, E. M., Cole, S. A., Cai, G., Proffitt, M., & Comuzzie, A. G. (2003). Estudios sobre genetica del sindrome metabolico y obesidad en un modelo de primates no humanos: potencial relevancia para la investigacion clinica y biomedica. *Revista de Endocrinologia y Nutricion, 11,* 120-128.

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Continued

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