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Computer Ranch Gains 5,000 More Processors

From initial processors stored in a closet, the "computer ranch" at the Southwest Foundation for Biomedical Research (SFBR) is more than doubling in size, thanks to a $2 million federal grant that will create new jobs as it speeds the pace of discovery at the Foundation's AT&T Genomics Computing Center.

The grant is funding the manufacture and installation of 5,004 more processors for the computing center. This will give the Foundation a total of 8,004 linked computers that can work in tandem to process the billions of calculations required for complex genetic analyses. Installation of the processors will be completed this fall.

The investment will add to the computing power of the ranch and provide a 20-fold increase in data storage capacity, said John Blangero, Ph.D., a statistical geneticist and director of the computing center.

Until recently, cost and technological limits meant that scientists had to focus any study on a limited sample of the genome. The field is advancing rapidly, though, and soon computational geneticists will be able to undertake complete genome sequencing of individual subjects in their studies, said Blangero.

"Our expansion will provide us with sufficient computational firepower to handle the coming flood of whole human genome sequencing, which will become cost-effective in the next one to two years," Blangero said. "This investment will keep the Foundation at the forefront of the expanding genetic frontier."

Funding for the expansion comes through the American Recovery and Reinvestment Act, part of the economic stimulus package approved by Congress in 2009. It provided money to the National Center for Research Resources, a part of the National Institutes of Health (NIH). The Foundation's grant application got a perfect score in the competitive review process, which considered both the equipment's effect on scientific research and its impact on job creation.

The Foundation will add one systems analyst position because of the computer expansion, Blangero said. M&A Technology Inc. of Carrollton, Texas, which is manufacturing, installing and maintaining the specialized processors, will add one or possibly two new positions because of its contract with the Foundation, said Senior Vice President Val Overbey Sr.

M&A Technology has sales and service operations in San Antonio. Formed in 1984, it has been the Foundation's partner since 2002 in designing, assembling and maintaining the computer ranch.

John Blangero, Ph.D., with Harald H. H. Göring, Ph.D., inside the AT&T Genomics Computing Center.

The computers support $110 million worth of NIH grants, giving the Foundation a compelling case in favor of the additional federal investment, said Blangero. "The decision was made that giving us $2 million to support our work was a good idea," he said. "We also showed that we had a need for expansion because of the cutting-edge computational activities that we are engaged in."

Foundation scientists are directing or supporting a number of studies that employ extended family pedigrees to track down the genetic basis of chronic complex diseases. These include the San Antonio Family Heart Study, begun at the Foundation in 1991, which has involved 1,400 Mexican Americans from 40 San Antonio-area families in the search for genes that influence heart disease, diabetes and obesity. The genetic data collected in that study has given rise to several others, including studies now looking at the genetic determinants of brain structure and the genetic basis of psychiatric illnesses. ■

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Letter from the Chief Scientific Officer

SFBR animal research saves lives worldwide

By John L. VandeBerg, Ph.D

Much of the progress achieved at the Southwest Foundation for Biomedical Research (SFBR) has been made possible by the rich animal resource at our Southwest National Primate Research Center (SNPRC). Our studies using special animal models are saving lives and bringing hope for improving human health worldwide. This research, which cannot be done in test tubes or computer simulations, addresses major threats to human health, including cancer, heart disease, AIDS, hepatitis and spinal cord injury.

Baboon: neonatal health, genetics of obesity and diabetes

SFBR has the world's largest captive population of baboons, approximately 2,100, which we developed as an animal model for biomedical research beginning in the 1950s. Baboons at SNPRC were used in neonatal studies that led to advances in respiratory therapy that have greatly improved the survival rates of premature infants worldwide.

Our Baboon Program Project, built on the pioneering efforts of SFBR researchers Nicholas T. Werthessen, Ph.D., and Henry McGill, M.D., continues to provide a unique opportunity for genetic analyses, due to the genetic similarity of baboons to humans, the large pedigrees that have been established, and the similarity in the way baboons develop cardiovascular disease. We have learned much about 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. The goal is to develop individually tailored diets and therapeutic drugs to help prevent and treat the disease, which is the No. 1 cause of death in the U.S.

A promising study in baboons by SFBR geneticist Anthony Comuzzie, Ph.D., is shedding new light on the effects of the typical American "junk food" diet. Another recent study published in the *Arteriosclerosis, Thrombosis and Vascular Biology Journal*, looks at genetic variation in the way endothelial cells lining the blood vessels respond to cholesterol. This work may someday help doctors identify those most at risk for cardiovascular disease so that they can provide therapies and recommended lifestyle changes.

Chimpanzee: hepatitis

SFBR played a major role in the battle against hepatitis in the development of vaccines for hepatitis A and B, with the help of our chimpanzees. In addition, chimpanzees are used at SFBR to develop drugs for treating hepatitis. A recent study by SFBR virologist Robert Lanford, Ph.D., received widespread attention for demonstrating that a new drug causes a dramatic reduction of the blood and liver levels of hepatitis C virus in infected chimpanzees. The DNA-based nucleic acid drug, developed by the company Santaris Pharma, captures a small RNA molecule in the liver, called microRNA122, which hepatitis C requires for replication in the body. The drug offers promise for replacing the harsh drug cocktails that those with hepatitis C now endure, often without success.

Monodelphis: skin cancer, heart disease, spinal cord repair

SFBR developed the *Monodelphis domestica* opossum as a laboratory cancer research model, including melanoma induced by ultraviolet sunlight, as well as human tumor growth and metastasis in infant opossoms. A new SFBR study with this animal, published in September in the *Journal of Lipid Research*, found a gene that can cause high levels of "bad" cholesterol to accumulate in the blood as a result of a high-cholesterol diet. It offers hope for reducing risk of cardiovascular disease in humans *(see story page 3)*. In work aimed at developing treatments for spinal cord injuries, SFBR researchers are investigating the ability of the infant opossums to heal severed or crushed spines.

Rhesus monkey: AIDS

This animal is a valuable model in the effort to develop therapies for AIDS because it can develop a simian version of the disease. SFBR researcher Marie-Claire Gauduin, Ph.D., is testing drugs for treating newborn rhesus macaques infected with simian immunodeficiency virus, with the goal of improving treatment of human babies infected by HIV-positive mothers before or shortly after birth.

Marmoset: biodefense therapies and vaccines, hepatitis C

This small primate is becoming a valuable replacement for larger primates, especially in the area of biodefense therapies and vaccines. SFBR studies overseen by Ricardo Carrion Jr., Ph.D., have included progress toward development of a vaccine for the Ebola virus and the repurposing of a breast cancer drug to treat another potential bioterror weapon, the hemorrhagic Junin virus.

As these examples demonstrate, our gifted scientists working with our animal resources have the potential to improve and save many millions of lives. And those who support this work should know that you are an important part of our ongoing mission to improve the health of people worldwide. You are making a positive difference, and fulfilling the promise of our mission to improve the health of our global community. ■

SFBR Science Update

Advances in heart disease, biodefense, genetics of brain disorders

SFBR scientists' discovery of a gene that causes elevated levels of bad cholesterol to accumulate in the blood as a result of a high-fat diet offers hope for improving risk-reduction strategies in humans.

The researchers found the gene in a strain of laboratory opossum, the *Monodelphis domestica*, which was developed as an animal research model at SFBR. Results of the study were published in the October issue of the *Journal of Lipid Research*.

"This research will improve our understanding of cholesterol metabolism and may shed light on why some people have high levels of bad cholesterol in blood while others do not when they consume cholesterol-enriched diets," said John L. VandeBerg, Ph.D., SFBR's chief scientific officer and senior author on the paper.

Scientists studied cholesterol genetics in the laboratory opossum, shown here with pups.

The opossum has normal blood levels of "bad" low-density lipoprotein (LDL) cholesterol when fed a standard low-cholesterol diet, but has extremely elevated levels of LDL cholesterol when fed a high-cholesterol diet. VandeBerg's team studied these high-responding opossums to identify the genes and the underlying mechanisms that control response to dietary cholesterol. Co-authors on the paper were Jeannie Chan, Ph.D., Michael C. Mahaney, Ph.D., Rampratap S. Kushwaha, Ph.D., and Jane F. VandeBerg in SFBR's Department of Genetics.

They analyzed various lipids, or fats, in blood and bile to find differences in cholesterol metabolites. They sequenced candidate genes of interest to find mutations, and determined the impact of each mutation by genetic analyses. That led to the discovery that the high responders have a defective ABCB4 gene. The ABCB4 gene encodes a protein known to transport fats from the liver into bile to facilitate excretion of cholesterol from the body. Malfunction of the ABCB4 protein was found to impair cholesterol excretion, causing bad cholesterol to accumulate in the blood when a high-cholesterol diet is consumed.

"This is the first report to show that ABCB4 has a role in controlling blood cholesterol levels in response to dietary cholesterol in an animal model," said VandeBerg.

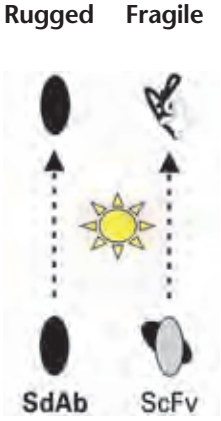
The next step is to determine whether ABCB4 mutations have an effect on levels of LDL cholesterol in humans who consume a high-cholesterol diet. "If we can identify early in life those people who are going to be adversely affected by consumption of high levels of cholesterol, we can encourage their parents and them to receive individually tailored counseling to establish dietary habits that protect them from cardiovascular disease," VandeBerg said.

The work was funded by the National Institutes of Health and the Robert J. Kleberg Jr. and Helen C. Kleberg Foundation.

Detecting neurotoxins

SFBR's Andrew Hayhurst, Ph.D., and his team have for the first time developed a highly sensitive means of detecting all seven types of botulinum neurotoxins (BoNTs) simultaneously. BoNTs are about 100 billion times more toxic than cyanide, and are on the federal list of potential bioterror threats alongside anthrax, Ebola virus and other infectious agents. The finding may lead to improved techniques for testing water and food supplies should BoNTs be used as a bioterrorism weapon.

The BoNT "detectives" are antibodies — proteins made by the body to fight diseases — found in llamas. The llama antibodies, called sdAb or "nanobodies," are very rugged, unlike conventional antibodies or their derivatives (scFv in the illustration). "As such, sdAb may allow biosensors to be used in harsh environments and also to be used over and over without loss of activity. Also, for some types of BoNT, conventional antibodies are not generally available and we are filling this biosecurity gap," said Hayhurst, an SFBR virologist. Since some sdAb have been shown to have inhibitory activity and can block toxin function, they may play a role as part of a future anti-botulism treatment.



Rugged llama sdAb are ideal biothreat detectives for austere environments.

The work, funded by the Defense Department's Defense Threat Reduction Agency Medical Diagnostics Program, is described in the journal *PLoS ONE*.

In the study, a llama was immunized with harmless versions of seven types of BoNT and blood then was taken to provide antibody-

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Ricardo Carrion Jr. works to make our future safer; appreciates SFBR scientific advances achieved years ago

Biosafety level 4 (BSL-4) laboratory Scientific Manager Ricardo Carrion Jr. helps our nation prepare for a dangerous future, but personally knows the value of SFBR's history. His son, born prematurely last October, spent months in neonatal intensive care receiving treatments that have improved over the years with the aid of research conducted at SFBR.

Carrion for the past seven years has managed the BSL-4 laboratory in the battle against deadly viruses. They include Ebola and the related Marburg, along with other federally listed "select agents," such as anthrax and plague.

Ricardo Carrion Jr.

San Antonio native Carrion, 39, is a spokesman for his home town's abundant opportunities for bioscience careers. "He mentors lots of junior people, and he's an excellent teacher," said Jean Patterson, Ph.D., Virology & Immunology chair for SFBR. "He's a role model for students at the Health Science Center. They can see that they can come from here and stay in the area and do high-quality research here."

Carrion grew up on San Antonio's South Side, graduated from Central Catholic High, and then earned a bachelor's degree from St. Mary's University, a master's degree from University of the Incarnate Word and a Ph.D. in microbiology and immunology at the University of Texas Health Science Center at San Antonio (UTHSCSA).

He has worked at SFBR for 13 years, beginning with his UTHSCSA dissertation, before joining the staff while doing postdoctoral work.

His mother, a teacher in the local Catholic school system, and father, a vice-principal in the Edgewood Independent School District, instilled in him a drive to learn and confidence to succeed.

Interest in research

Carrion fell in love with lab research while studying for his master's. While working on his Ph.D., he studied in Patterson's leishmaniavirus research program, and once in the BSL-4 lab, he was hooked on it.

The lab works on preventive vaccines, treatments for those infected, and diagnostics to identify pathogens in the environment. Federal anti-bioterror funding in recent years has included grants from the National Institutes of Health (NIH), Department of Defense and the Defense Threat Reduction Agency.

The lab fulfills an increasingly important role in advancing research, because a backlog in federal facilities has made it difficult for scientists to find a place to test compounds.

"The experiments that we're doing would not be done otherwise, or at least not in a timely fashion," Carrion said. "There is limited BSL-4 laboratory space at other facilities. As a private, nonprofit organization, we're able to take on these other projects that fit within our broad mission of improving the health of the global community. I think we play an important role in helping get these new vaccines and diagnostics out there, that otherwise are going to be sitting on the shelf."

A Lassa fever vaccine that SFBR started working on in 2003 had been in a scientist's freezer for 10 years, while he waited for a lab. Now that research at SFBR has determined that the vaccine works in non-human primates, the team is looking for collaborators to obtain additional funding to move it forward.

The lab also helps small companies perform proof-of-concept studies through "Small Business Innovation Research" grants from the NIH.

Carrion's experience with his premature son, Ricardo III, has made him keenly aware of the benefits of research conducted at SFBR over the past 30 years. The Foundation's development of the baboon as a model for neonatal care has played an important role in improving survival rates.

"Richie III" weighed 1 pound, 15 ounces, when born 16 weeks before his due date. Nearly a year later, he thrives at more than 18 pounds, and shows above-average cognitive development for his adjusted age.

Better neonatal care

SFBR's contributions to neonatal intensive care began in the early 1980s, when Henry McGill, M.D., examined prematurely born baboons that did not survive, and found lung disease. He showed the lungs to Jacqueline Coalson, Ph.D., a pathologist at UTHSCSA, who confirmed a condition identical to that found in human preemies.

That led to development of a neonatal intensive care unit at the Foundation, studying the baboon as a model for lung disease in premature infants. Initially the group, led by the late Robert deLemos, M.D., studied how ventilators injure lungs. SFBR researchers refined high-frequency oscillatory ventilation (HFOV), a gentler way of helping babies breathe, by delivering soft, tiny breaths several hundred times per minute. HFOV became a well established means of rescuing infants.

Richie received nasal CPAP (continuous positive airway pressure), a ventilatory method that avoids the lung damage that even HFOV can cause. Coalson and others at SFBR, including British neonatologist Merran Thompson, M.D., conducted extensive research with baboons that helped bring about refinements to nasal CPAP therapy.

BSL-4 lab receives upgrades during annual maintenance shutdown

SFBR's biosafety level 4 laboratory undergoes maintenance each year that includes upgrades to enhance safety and increase productivity. The lab is pumped full of hydrogen peroxide vapor to decontaminate the room.

It is an important annual event for the BSL-4 lab where scientists wearing air-tight "space suits" conduct research on Ebola and other deadly pathogens for which medicine has not yet found a cure. The annual hiatus in research at the lab offers a time for reviewing emergency procedures, thorough cleaning, essential maintenance checks on safety systems and other equipment, and physical modifications such as moving work stations or adding new equipment. Any of these activities are difficult to perform while the lab is "hot," when active research requires full activation of the containment systems and use of the protective suits.

"We even replace all the light bulbs because once you're hot, you can't even change a light bulb," said Jean Patterson, Ph.D., chair of the Department of Virology and Immunology. "The main purpose is that we want to make sure all the equipment is in good shape."

That includes the freezers where samples of the deadly biological agents studied in the lab are stored.

"Changing out a freezer is a huge undertaking," she said. "If a freezer goes down, then we rush in there and we try to find a location in another freezer."

That requires revising inventory records because of the need to account for everything.

ENV Services, a company with expertise in equipment certification, examines and calibrates all of the filters and safety devices to ensure that they are up to specifications and operating properly.

However, before the equipment can be checked, the laboratory must undergo a complete decontamination. Bioquell, a British company that specializes in decontamination of

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"Our family has directly benefited from the research performed in the baboon neonatal intensive care unit at SFBR," Carrion said. "The information gained about the use of CPAP to minimize lung injury in pre-term baboons has contributed to the approach to treating micro-preemies in neonatal intensive care units across the country. The CPAP data generated at SFBR provided scientific evidence for the rapid weaning of pre-term infants off ventilators and onto CPAP in order to prevent ventilator-induced lung damage and bronchopulmonary dysplasia."

Before establishment of the baboon model, "there was really no way to advance the way these babies were being managed," said former SFBR researcher Thomas Kuehl, Ph.D., a reproductive biologist and professor at the Texas A&M Medical School branch at Scott and White Hospital in Temple, who worked with McGill and deLemos.

"Research at SFBR really changed the management systems used for pre-term neonates by creating an animal model that allowed for experimentation with ventilators, nutrient supplements, solutions and antibiotics, where you could follow up and look at the long-term effects," Kuehl said. "An observation that could not be made in children could be done in animal models, and that made it possible to find ways to do things differently if we needed to."

Away from SFBR, Carrion stays grounded. Saturday nights and Sundays at noon, he plays the organ with the St. Philip of Jesus Catholic Church choir, with his brother-in-law on keyboard and his choir director father. Carrion has been church organist since the age of 10. His photography hobby lately has been focused on little Richie III.

"We know that Richie's good outcome is due in part to the advances made at SFBR and for this we are profoundly grateful."
— Ricardo Carrion Jr.

His wife, Tricia, a registered nurse, has been taking time off to take care of the baby.

In addition to scientists whose research contributed to his son's recovery, the Carrions are thankful for donors supporting SFBR's research. "We know that Richie's good outcome is due in part to the advances made at SFBR," he said, "and for this we are profoundly grateful." ■

BSL-4 shutdown includes safety review, equipment upgrades

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laboratories, buildings and equipment, supervises the set up of generators that produce a highly concentrated hydrogen peroxide vapor that penetrates everything inside the lab. The concentration of hydrogen peroxide is much higher than the liquid antiseptic solution available at retail stores for treating minor wounds.

To make sure that anything possibly dangerous is inactivated, packets containing spores of harmless *Geobacillus stearothermophilus* are placed throughout the lab. Because spores are among the most difficult things to kill, they provide a good test of the lab cleansing's effectiveness. Packets of spores are placed in hidden locations, such as underneath cabinets and inside equipment. After the treatment with hydrogen peroxide, the spores are placed in growth media to make sure they are dead.

After a week of negative readings, the lab opens up for the maintenance and safety review and any modifications.

Ricardo Carrion Jr., Ph.D., the lab's scientific manager, said the hydrogen peroxide treatment is far superior to the previous reliance on highly corrosive formaldehyde, which would damage electronic equipment and even the copper coils on the freezers where the biological samples are stored. That does not happen with hydrogen peroxide. Nor do the cleaners need to bag up all of the electronics like they used to. Hydrogen peroxide does cause bubbling of paint, but that is not considered a serious problem.

The use of hydrogen peroxide as a biocide also offers a "greener" procedure. The vapor breaks down to water vapor and oxygen.

Safety review

Every year during this time, the hazardous materials team, fire department, police and Federal Bureau of Investigation (FBI) visit the lab to observe mock rescue procedures of "injured" people in their lab suits placed upon backboards and taken out of the lab. The agencies provide input on how SFBR could improve techniques. The Foundation also gives these public safety officials an overview of its research programs, as well as an orientation on the size of the campus and locations of animals and chemicals.

The Department of Virology and Immunology meets more often than once a year with the FBI, in order to keep the agency familiar with what type of research the Foundation does, and with the layout of the laboratories in case they ever would need to respond quickly.

"Our staff is trained on how to evacuate somebody," Carrion said. "We haven't needed to pull anybody out. But in case we do, we like to think that our people are trained to be able to do that, because the FBI, hazardous materials, fire and police teams will not go into our BSL-4 lab. It's our job to remove them from the lab and we train our staff to do that."

SFBR's BSL-4 lab

"It's a process that we do that's important, just to be prepared."

Equipment upgrades

The actual work on the facility and equipment this year was more extensive than usual, due to the installation of new breathing-air compressors for the scientists, who must be tethered to air hoses at all times in the lab. The new compressors will allow for a doubling of the number of scientists who could possibly work in the lab at the same time, from the previous limit of four, to eight. However, the lab won't usually have more than six people in it at a time, Carrion said.

Another new feature added this time is the digital display board that will run live news tickers from the Homeland Security Channel, and show biosafety presentations to remind the lab workers of best practices, such as keeping hands inside the biosafety cabinets and avoiding re-capping of needles and other hazardous procedures.

"But mainly, it's a backup safety device," Carrion said. "If our radio communication were to go out, we could scroll information to them, such as: 'The radios are out. Exit the lab now.'" ■

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producing cells. Using bioengineering techniques, the antibody genes were cloned and the resulting antibodies were tested for their ability to detect BoNT in a selection of drinks, including milk. Hayhurst and his team are continuing to study the molecular interactions of the llama antibodies to find out why they are so specific and why some of them inhibit toxins.

The laboratory capabilities of SFBR enabled this research to be performed according to all applicable federal guidelines of biosafety and biosecurity under the federal Centers for Disease Control and Prevention Select Agent Program.

Finding clues to brain disorders

Scientists at SFBR and the University of Texas Health Science Center at San Antonio are performing cutting-edge research in genetics, trying to pinpoint which genes influence the risk of health problems such as depression, Alzheimer's, attention deficit hyperactivity disorder and schizophrenia. They are using brain scans to determine what is normal, looking at brain formations and functions, showing which areas of the brain "light up" when certain tasks are performed and when a person is at rest.

Genetics plays a role in what is called the "default mode" network, the regions of the brain used when people are day-dreaming or letting their minds wander. Abnormalities in the default mode network can influence interpersonal interactions and decisions and how people cope with their environment.

Thousands of scans in San Antonio are being processed at the Southwest Foundation for Biomedical Research, where analytical software and a giant computer system are utilized to identify specific genes. This effort could eventually give doctors markers for these mysterious psychiatric and neurological illnesses.

The scans are analyzed at SFBR's AT&T Genomics Computing Center, which is overseen by John Blangero, Ph.D. The center houses the world's largest computer cluster for human genetic and genomic research, which allows scientists to search for disease-influencing genes at record speed.

A study published in the *Proceedings of the National Academy of Sciences* offered evidence that genetics plays a role in what is called the "default mode" network, the regions of the brain used when people are day-dreaming or letting their minds wander. Abnormalities in the default mode network can influence interpersonal interactions and decisions and how people cope with their environment.

The brain is one of the final frontiers of modern medicine. Using images to help crack the genetic code of inherited tendencies could revolutionize how many diseases are diagnosed and eventually treated. ■

Southwest Foundation Forum Gala

The 40th annual Southwest Foundation Forum Gala on May 1, 2010 raised $160,000 for pilot research studies at SFBR. The evening's theme was Esplendores de la Cultura Mexicana, with accompanying décor, food and entertainment. In the photo, left to right, are Mary Beth Mosbacker, gala co-chair; Kathleen LeFlore, gala assistant; and and Paola Lloyd, gala chair. Raffle items included vacations to Puerto Vallarta and Napa Valley.

SFBR National Advisory Board Members First Meeting

The first meeting of SFBR's newly appointed national advisory board met April 14 -16 on the Foundation campus. In June, the board issued a report that contained constructive suggestions for how the Foundation might enhance its research and administrative infrastructure. Left to right, are Kenneth Shine, M.D.; Richard Doughty, M.S., C.M.A.; Margaret Kripke, Ph.D.; Board Chair Robert Mahley, M.D., Ph.D.; Claude Bouchard, Ph.D.; and James LeDuc, Ph.D.

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