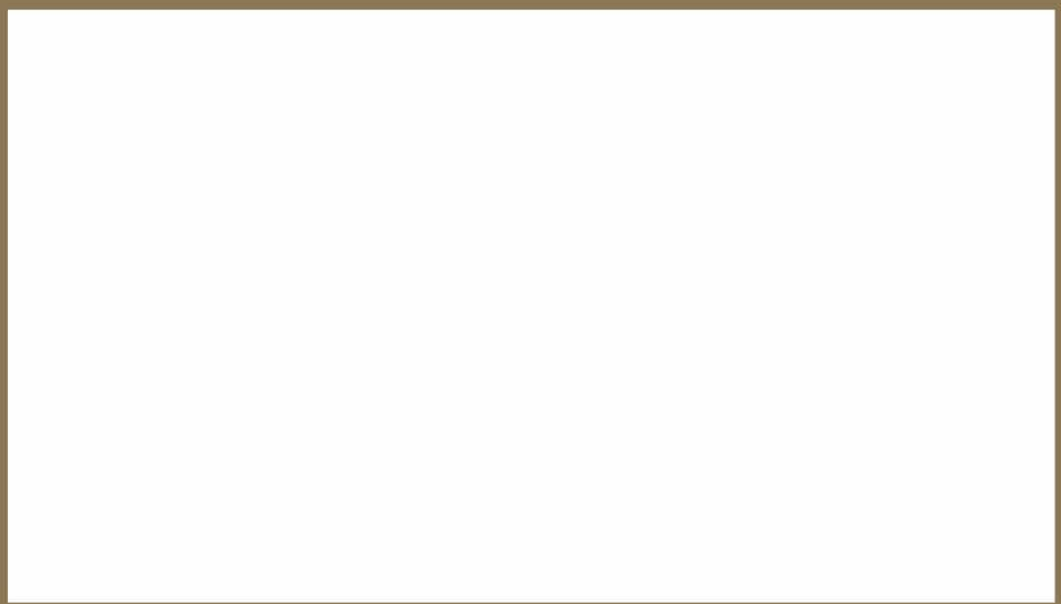
GLOBAL IMPACT

TEXAS BIOMEDICAL RESEARCH INSTITUTE

2014 Annual Report



Texas Biomedical Research Institute

2014 Annual Report

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Structural studies of the drug oxamniquine (3D stick representation) and its sulfotransferase target are being used to develop improved therapies against parasitic blood flukes (Schistosoma spp.) that infect over 200 million people worldwide. Research on schistosomiasis is being done in Dr. Tim Anderson's laboratory, Texas Biomed Department of Genetics, in collaboration with scientists from the UT Health Science Center at San Antonio (UTHSCSA). Image provided by John Hart, UTHSCSA

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ROBERT W. GRACY, PH.D.

A LETTER FROM THE **PRESIDENT**

In 2014, Texas Biomed made a significant impact toward combatting human disease and improving the future of human health. It is with great regard I think about the people and the passion that comprise this Institution. People are at the heart of our mission… enhancing lives through discovery.

As an independent, not-for-profit, research institution, Texas Biomed uniquely provides a greater understanding of health and makes discoveries that lead to better diagnostics, preventions, therapies and cures for a number of diseases impacting millions of lives.

What does that impact look like? Let's take a look at the numbers.

Ebola virus spreading through West Africa was a defining moment last year. More than 11,000 people have died so far from the outbreak that began in March 2014. According to the World Health Organization, more than 584,000 people died from malaria in 2013. In the United States, more than 1.1 million people are living with HIV. One in three Americans dies of heart disease, and about 50,000 Americans are diagnosed with Parkinson's disease annually, just to name a few.

We recognize that these are not simply numbers but lives lost and families and communities impacted. And, it is with this in mind that we seek answers to scientific questions that can change our world.

As the world struggles with these diseases, scientists at Texas Biomed are making major progress in the fight. Collaborations with pharmaceutical companies in the advancement of vaccines against Ebola virus have progressed to human trials in 2015. A new method for sequencing the genomes of individual malaria parasites holds the promise of the design of drugs and vaccines against malaria. Scientists at Texas Biomed have identified new possibilities in vaccine development to protect against the spread of HIV. And, the addition of a regenerative medicine program is working toward drug development and therapies against neurodegenerative disorders, like Parkinson's disease.

These exciting discoveries belong to all of us. We are able to make progress thanks to our many generous supporters and the vision of our Board of Trustees. This vision, to create a world-class institution dedicated to the scientific advancement of human health, began with our Founder, Thomas Baker Slick, Jr. He saw the impact that science could have on mankind, and together, we are making his vision a reality.

Robert W. Gracy,
Ph.D., President and CEO

Texas Biomed Scientific Leadership Team (pictured left to right): Dr. Michael Olivier was named Chair, Department of Genetics, in September 2014; Dr. Jean Patterson, Chair, Department of Virology & Immunology; Dr. Robert W. Gracy was named President and CEO in July 2014; Dr. Robert Lanford was named Southwest National Primate Research Center Director in March 2014.

> We recognize that these are not simply numbers but lives lost and families and communities impacted. And, it is with this in mind that we seek answers to scientific questions that can change our world.

TEXAS BIOMED'S **IMPACT**

INNOVATION. Invention is a way of life at Texas Biomedical Research Institute. As an independent research institution of nearly 75 years, Texas Biomed has the foundation and flexibility to support advances in human health with unique research in genetics, virology and immunology, regenerative medicine, aging and much more. The Texas Biomed team seeks answers to some of the world's most puzzling health questions so that one day we can fully cure or prevent disease.

MOTIVATION. Inspired by the philanthropic vision of our founder, Thomas B. Slick, Jr., in 1941, Texas Biomed is host to many unique resources, not the least of which are our people. Our team of doctoral-level scientists continuously seek new ways to study hundreds of diseases that impact millions of lives, and our team of more than 350 people are motivated by progress.

PASSION. Scientific discoveries require the support of our entire community, and Texas Biomed is thankful to the thousands of philanthropic supporters who advance our science and our scientists. About 70 percent of the Institute's annual budget is funded from highly competitive, peer-reviewed federal research grants and contracts. Philanthropy constitutes the second-largest portion of the Institute's budget with nearly 20 percent of Texas Biomed's expenses met by the generous contributions of foundations, corporations, and individuals, as well as income from Texas Biomed's endowment and royalties.

ASSETS. Excellence requires a commitment to developing our talent and resources. The Institute has the nation's only privately owned biosafety level 4 laboratory. Designed for maximum containment, the BSL-4 lab allows Texas Biomed investigators to safely study deadly pathogens for which there currently are no treatments or vaccines. Texas Biomed is also home to the Southwest National Primate Research Center and the world's largest baboon research colony, including a unique pedigreed baboon colony that is invaluable for genetic studies on complex diseases. The Institute enjoys a distinguished history in the innovative, humane, and appropriate use of nonhuman primates in biomedical research. In addition, the AT&T Genomics Computing Center is one of the world's largest computing clusters dedicated exclusively to human disease genetics research.

COMPLEXITY. The complex demands on biomedical research are numerous. From declining national dollars dedicated to scientific research to worldwide outbreaks of new and recognized viruses for which there are still no cures to national disease epidemics such as obesity and diabetes threatening millions of lives, these challenges can seem overwhelming, but at Texas Biomed, we know that together, we can overcome and discover groundbreaking solutions.

TEAMWORK. A foundation built on cooperation and collaboration is necessary to develop the solutions we need. The Institute partners with hundreds of researchers and institutions around the world, pursuing advances in the prevention and treatment of heart disease, diabetes, obesity, osteoporosis, AIDS, hepatitis, malaria, Ebola virus, Parkinson's disease, Macular Degeneration, parasitic infections and many other diseases. Together, our people and our passion are making a global impact!

> The Texas Biomed team seeks answers to some of the world's most puzzling health questions so that one day we can fully cure or prevent disease.

For more information about Texas Biomedical Research Institute and its efforts to improve human health, contact the Institute at 210-258-9400 or visit the Website at www.TxBiomed.org.

FIGHTING EBOLA VIRUS

CHANGING THE WORLD, ONE DISCOVERY AT A TIME.

Last year, the Ebola virus disease outbreak overcame West Africa and spilled into the U.S. when an individual who traveled from Liberia was admitted to a Texas hospital with Ebola virus infection. For scientists in Texas Biomed's Department of Virology and Immunology (V&I), where they have been conducting experiments on Ebola virus for more than ten years, "It was business as usual," said Department Chair Dr. Jean Patterson.

With its BioSafety Level – 4 (BSL-4) facilities and nonhuman primate colonies, Texas Biomed has long been at the forefront of research on many dangerous viruses. In fact, Texas Biomed scientists had been conducting tests to verify the most promising candidate vaccines since 2007, but as of the outbreak, a viable vaccine candidate had proven elusive.

As is often the case in science, a failure is never truly a failure when it leads to greater understanding of the disease process and ultimately, promises new hope. Though initial tests on one particular vaccine were hopeful, when Texas Biomed scientists attempted to replicate results in other animals that more closely mimicked human disease, they found that the animal models used with the particular virus strains did not completely address the entire story.

"We realized that the animal model wasn't characterized as well as it should have been," said Dr. Ricardo Carrion, V&I Associate Scientist & BSL-4 Lab Scientific Manager.

(Pictured from L to R) Dr. Ricardo Carrion, Jr., Dr. Robert Davey, Dr. Luis Giavedoni, Dr. Jean Patterson, Dr. Andrew Hayhurst, Dr. Anthony Griffiths

This information proved invaluable, as it allowed the team to characterize the virus more completely, which in turn helped to determine which factors were most important. In the process, they developed better animal models with viral strains that could relate more closely to the disease process in humans.

According to Carrion, "Had we not had a vaccine failure, we would not be at the advanced stage we are now in developing a vaccine."

Vaccines take years to develop and even longer to determine safety. Studying lethal pathogens in a large animal requires a significant amount of space. Over the past few years, the BSL-4 lab had been modified to accommodate more animals and more studies. This also meant that staff adjusted to a 24/7 work cycle, with scientists blocking time to conduct experiments at all hours of the day and night.

In the current BSL-4 lab at Texas Biomed, V&I scientists established a higher throughput system to screen vaccine candidates. The other BSL-4 laboratories in the U.S. have specific missions, thus limiting their ability to test vaccines. Texas Biomed, as the only privately-owned BSL-4 lab, can shift its priorities to fill that void. Additionally, the scientific expertise, advanced standard operating procedures, quality systems and virus stocks make Texas Biomed a preferrable lab. When the demand came for enhanced vaccine studies in the wake of the 2014 Ebola virus disease outbreak, scientists worldwide turned to the expertise at Texas Biomed.

"We are viewed as the best program for quality research because we incorporate critiques to continually improve the research process," Patterson said.

Scientists in the V&I Department are part of an Ebola Working Group facilitated via the National Institutes of Health and the Department of Defense. The existence of such a team means that viruses and knowledge are shared amongst testing sites. Thus, concerted efforts to characterize the virus, develop assays and evaluate the vaccine candidates have improved the research overall. When each site gets the same results, the validity of those results is enhanced.

Developing any vaccine requires an understanding of how the host's immune system responds to the virus and to the potential vaccine. That's where Dr. Luis Giavedoni, Scientist and Vice Chair of V&I, comes in. In the Immunology Core Laboratory of the Southwest National Primate Research Center, his team has been verifying the candidate vaccines to see if they elicit the expected immune responses. The immune status of the animal must be characterized prior to challenge by the virus, and then followed while the animal is in the BSL-4 lab.

"We can then correlate these data to guide vaccine trials in humans," said Giavedoni. Aside from his Ebola vaccine efforts, he is also studying potential AIDS vaccines using the simian immunodeficiency virus (SIV) in rhesus macaques.

The physical limits of the BSL-4 lab space prevent further ramping up of vaccine studies. However, the race to identify drug targets for Ebola and other pathogens has meant a near 20-fold increase in workload this past year in the lab of Dr. Robert Davey, V&I Scientist and Ewing Halsell Scholar. Among those small molecules identified this past year was Tetrandrine, from the Chinese herb *Stephania tetrandra*. This compound blocks the "Two Pore Channels" (TPCs) necessary for Ebola virus to traverse the cell. Having identified the cellular function of this compound, early tests in mice showed that it blocked Ebola infection.

Davey's findings were featured as the cover article in the journal *Science* in early 2015, and he was recognized as a San Antonio Healthcare Hero. The research does not stop here, of course. The next step will be to conduct tests on animal models that mimic human disease. Time is critical in the search for a cure for Ebola, and private support has been essential in moving Davey's research forward.

Early detection of Ebola virus disease is vital to treatment. Dr. Andrew Hayhurst, V&I Associate Scientist, has developed novel llama antibody libraries capable of targeting any chosen virus. Using this resource, his lab identified antibodies that recognized a small conserved region of a protein in Marburg virus with a very similar architecture to Ebola virus. This recognition could pave the way for early identification testing kits that can be used in the field.

Current testing methods for Ebola are only accurate in the later stages of the disease, usually well after an outbreak is in full swing. Developing a tool which is not dependent upon refrigeration and can identify Ebola virus early in infection can stop an outbreak in its tracks. A new National Institutes of Health R01 grant in 2015 will enable his team to further this research over the next five years.

Ebola virus dominated headlines and the minds of many of the world's infectious disease scientists. Texas Biomed was already in a prime position to push this research forward. But Ebola isn't the only lethal pathogen studied here. In addition to long-standing research on HIV, V&I scientists are conducting research on other hemorrhagic fever viruses including Lassa Fever Virus, Crimean-Congo Hemorrhagic Fever Virus, and other Filoviruses. They are also initiating studies on South American Arenaviruses and Alphaviruses.

While Ebola's high fatality rate terrified the world, the most important lesson learned was that what happens in one part of the world has the potential to affect us all.

"We can take care of people who get sick here in the U.S., but we need to stop the outbreaks where they exist. Much of our work is focused on stopping the disease at the source," Dr. Patterson said.

NONHUMAN PRIMATES AND LIVESAVING DISCOVERIES

CHANGING THE WORLD, ONE DISCOVERY AT A TIME.

As one of only seven national primate research centers, the Southwest National Primate Research Center (SNPRC) is part of a nationwide consortium of institutions dedicated to advancing science through research with nonhuman primates. This research has led to a greater understanding of and treatments for diseases such as hepatitis, HIV, Ebola virus, diabetes, cardiovascular disease and so much more.

As people seek to understand how we can better treat or cure human diseases, more commonly referred to as translational medicine, nonhuman primate models are becoming increasingly more important.

In a recent paper authored by Texas Biomed Scientists Dr. Marcel M. Daadi, Dr. Tiziano Barberi, Dr. Qiang Shi, and Dr. Robert E. Lanford, published in *Stem Cells and Development*, Daadi states, "Humans and nonhuman primates (NHPs) are similar in size, behavior, physiology, biochemistry, structure and function of organs, and complexity of the immune system. Research on NHPs generates complementary data that bridge translational research from small animal models to humans."

Texas Biomedical Research Institute launched a new regenerative medicine program in 2014 with the addition of Daadi and Barberi. Renowned in the field of stem cell science, these scientists both stated that key to their decision to join the Texas Biomed team was the unique resource provided by the primate center.

According to the International Society for Stem Cell Research, regenerative medicine focuses on "medical interventions that aim to repair damaged organs, most often by using stem cells to replace cells and tissues damaged by aging and by disease."

Dr. Suzette Tardif

Dr. Marcel Daadi

Dr. Tiziano Barberi and Dr. Bianca Borchin

Daadi and Barberi are working on a variety of interventions for such diseases as neurodegenerative disorders like Parkinson's Disease, stroke and traumatic brain injury as well as muscular disorders like Muscular Dystrophy and diseases of the eye such as Macular Degeneration.

In order to ensure these stem cell therapies are safe and effective, researchers must first prove they work in a nonhuman primate model.

"The ultimate goal of safety and efficacy studies in nonhuman primate models is to better predict outcomes, address challenges and increase the likelihood of success in human clinical trials," Daadi states in the *Stem Cells and Developement* paper. "Research on nonhuman primates can generate complementary data that bridge translational research from small animal models to humans."

Regenerative medicine is just one way in which nonhuman primate models are critical to combatting human disease. Texas Biomed's Department of Genetics looks at new ways to identify and discover gene targets and gene therapies for obesity, diabetes, atherosclerosis and other chronic diseases. Nonhuman primate models are as critical to this effort as they are to the testing of potential vaccines and cures for deadly pathogens, such as Ebola virus, hepatitis viruses and HIV.

Nonhuman primate models may also hold the key to identifying ways we can slow down the aging process and thus age-related diseases, like cardiovascular disease, Alzheimer's, osteoporosis and much more.

Dr. Suzette Tardif joined the Southwest National Primate Research Center in 2014 as the Associate Director of Research. Tardif's research has focused for more than 30 years on developing the common marmoset monkey as a biomedical model for disease.

Through a partnership with the Barshop Institute for Longevity and Aging Studies at the University of Texas Health Science Center at San Antonio, Tardif is working with collaborators to develop the marmoset as an efficient model in which to study aging. Studies have already shown positive results of one particular pharmaceutical intervention called Rapamycin. The drug was originally shown in 2009 to reliably increase lifespan in a rodent model; however, moving from rodents to humans requires greater study of the drug's effectiveness, as well as its safety in a model more closely related to humans.

"We recently reported our ability to rapidly and reliably dose socially-housed marmosets with an oral form of Rapamycin that is well tolerated and results in suppression of the mTOR pathway," Tardif said. "Specifically, we have to study the effect of aging interventions on the healthy lifespan of a primate."

From stem cell therapy to gene therapy to pharmaceutical interventions for disease, the Southwest National Primate Research Center allows for the humane study of diseases and is a critical step in the process to advancing human health.

"We, as scientists and as citizens, understand that we must carefully consider our use of nonhuman primates in all research, but it is inherently clear that nonhuman primates were critical in helping us eliminate diseases of the past and will continue to be necessary to curing diseases of the future," said Dr. Robert Lanford, Director of the Southwest National Primate Research Center. "We are passionate about being good stewards of such a critical resource and excited to be a vital link in the process of moving basic research from the lab to the bedside."

FUTURE OF GENETICS AT TEXAS BIOMED

CHANGING THE WORLD, ONE DISCOVERY AT A TIME.

The study of genetics is always evolving, nowhere more so than at Texas Biomed. Traditionally, geneticists have focused on finding the changes in genetic sequences that correlated with diseases or traits related to diseases. For example, work would focus on which gene variants are responsible for regulating glucose levels leading to diabetes or what genetic change affects a person's risk for high cholesterol.

Dr. Michael Olivier, Chair of the Department of Genetics, explained how we currently understand and use genetics and where it is headed.

"Like a Lego™ kit, our DNA is made of building blocks. For example, to build a car, you need the building blocks and the manual. Thanks to all the statistical analyses we have historically done in genetics research, we now have a manual to our genetic code and can read it," Olivier said. "But, what we don't know is whether a Lego kit where not all the pieces perfectly match the manual or some might be missing will result in a different product at the end. How does a small genetic change make a difference in how we express that gene? And, does that change make a difference for developing specific diseases?"

The next step in genetics research is to answer that question, How? How does a specific mutation change the outcome at the molecular level? How does the cell respond to the genetic change?

The challenge is to investigate the molecular and cellular steps leading up to the final outcome, essentially testing whether putting that red Lego piece where a blue one was supposed to go makes the Lego car run differently.

Historically, Texas Biomed genetics research has focused on statistical analyses, which has provided a firm foundation for the study of genetic diseases. Now, scientists at Texas Biomed are in a unique position to understand the entire picture. They can combine the expertise of protein science, metabolic science, genetics and complex data integration and analysis with high throughput instrumentation, such as a mass spectrometer. This expertise is not typically available to a genetics group all under one roof.

Collaboration and cooperation is the key to continued success. One such area of collaboration includes the new regenerative medicine program at the Southwest National Primate Research Center at Texas Biomed.

Dr. Michael Olivier and Dr. Laura Cox

In the past, geneticists used transformed cells whose genetic makeup has been altered to study genetic changes. However, such cells have been altered substantially and therefore do not behave normally. As a result, it can be difficult to interpret the actual effect on cell function.

Induced Pluripotent Stem Cells (iPSCs) are cells that can differentiate into any type of cell and come from adult, rather than embryonic, tissue. Using iPSCs, scientists can induce a genetic mutation, and then study the cell as it progresses to its final stage, gaining insight into the molecular and cellular steps that lead to the different phenotype.

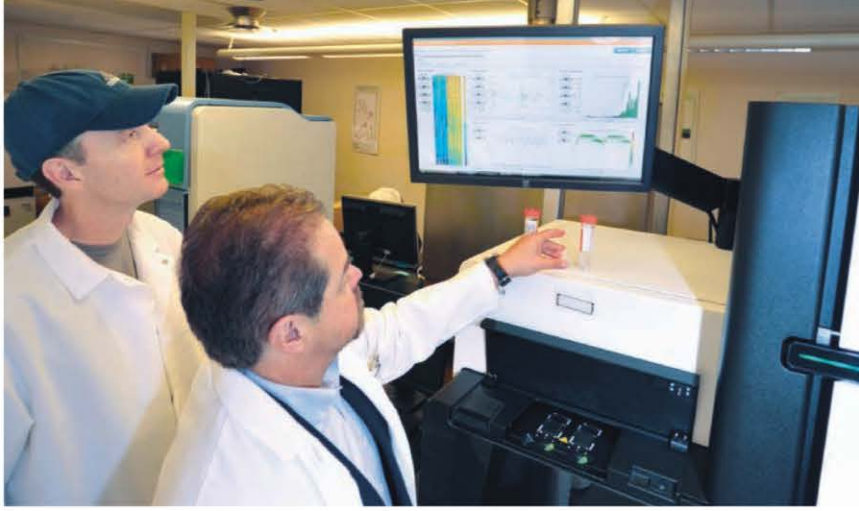
Using the Lego analogy, "This new technology means scientists can change one block of that Lego car, and see what happens," Olivier said.

In the past, such studies would take months to simply develop the appropriate cell line before initiating the experiments. One significant advantage of iPSC technology is that the development process is condensed into a much shorter time frame. This will lead to more rapid identification of potential targets for new drugs for treatment and recommendations for prevention of a variety of genetic disorders.

The scientists at Texas Biomed are also taking advantage of Next Generation Sequencing (NGS), which overcomes previous issues of throughput, scalability, speed and resolution. The Department has been awarded a grant that will allow them to sequence 700 genomes of baboons from the pedigreed colony.

"This resource will be a game changer," said Dr. Laura Cox, Scientist and Vice Chair of the Department of Genetics. "In the past, scientists relied upon large-scale population studies. Now they will be able to start with known genome sequences as the initial selection criteria when conducting studies."

Work on early-stage human and nonhuman primate genetic research provides the foundation necessary for scientists to conduct translational research, the ultimate focus of researchers at Texas Biomed — taking science from the lab to the individual.



> Like a Lego™ kit, our DNA is made of building blocks.
> — Dr. Michael Olivier

A collaboration that began in 2014 with the national organization Take Off Pounds Sensibly (TOPS) aims to look specifically at individual outcomes in a unique way. Texas Biomed has partnered with TOPS to begin work on a study that will identify individuals within families who, despite being exposed to the same lifestyle choices, do not gain weight, or individuals that have managed to lose weight and not gain it again. What makes these individuals different?

The study will focus on the interaction of food, behavior and genetics and try to answer questions about why one individual does not have the same reaction to food as another person.

Over the years, Texas Biomed scientists have gained a wealth of information about the genetics of obesity. By collaborating with local initiatives for health and wellness, such as Take Off Pounds Sensibly (TOPS), these organizations can make the most of the scientific expertise of Texas Biomed as an individual progresses on his or her journey to a healthier lifestyle.

Combining advanced technology in genetics research with programs using the outcome of that research in practical situations continues to place Texas Biomed scientists at the forefront of health and science.

2014 RESEARCH BRIEFS

MALARIA

Malaria continues to be an enormous problem throughout the world, with up to 500 million people infected annually and more than 2 million of those dying from the disease. The disease has a great impact on not only the health of a country but also on the education of its people and the economic health of that country. In our interconnected global village, a healthy economy affects us all.

The disease is caused by multiple parasites that have a long history of evolution with their hosts, with two species, *Plasmodium (P.) falciparum* and *P. vivax*, causing the most disease in humans. The parasites have proven to be canny, developing resistance to each of the five classes of drugs currently available.

To gain the advantage on these malaria parasites, scientists at Texas Biomed have been studying the mutations that lead to drug resistance. In the past, this required isolation of individual parasite clones from human infections, then analysis of their genetic differences. This labor-intensive task was slow and yielded very small quantities of DNA. Because infections are often mixed with multiple parasite clones, it is difficult to separate individual parasites. "It's like trying to understand human genetics by taking DNA from everyone in a village at once. The data are all jumbled up — what we really want is information from individuals," Dr. Ian Cheeseman, Staff Scientist in the Department of Genetics, said. Furthermore, since *P. vivax* cannot be grown in culture, all research was focused on *P. falciparum*.

Cheeseman and his team are making the most of new technology to tease out these genetic differences. By using fluorescent dyes, they can separate the parasite-infected red blood cells from the uninfected red blood cells by flow cytometry. This allows them to focus on only those cells that contain parasites with extremely small quantities of DNA. This method does not rely on growing the parasite in a cell culture, so studies can also be performed on *P. vivax*, a huge boost to research capabilities.

By identifying the mutations leading to drug resistance in both *P. falciparum* and *P. vivax*, the scientists have the potential to develop better treatment options and potential vaccine targets.

Dr. Ian Cheeseman

MATERNAL NUTRITION STUDY

Malnutrition is a significant problem worldwide, but also in the U.S., where more than 50 million Americans live in households with insufficient food. Scientists have long known that nutrient deficiency in pregnancy has a negative impact upon developing organs, but until now very little has been known about the impact on the developing brain. The long-held theory was that when deprived of sufficient calorie intake, the other organs would suffer to protect the primate brain.

New research by Texas Biomed's Dr. Laura Cox, Scientist and Vice Chair in the Department of Genetics, and her colleagues at the University of Wyoming has indicated that the frontal cortex is also affected when the pregnant mother experiences nutrient deficiency. Because they can study this in nonhuman primates, Texas Biomed scientists have learned a great deal more about brain development than they could with the rodent models previously studied.

When pregnant baboons were fed a diet with 30 percent fewer calories than normal, they found very little effect in the brain stem. However, when they examined the frontal cortex, the center for higher order thinking and cognition, they found more significant changes. In the offspring, behavioral studies show greater impulsivity and decreased attention span in males, whereas in females, the effects were marginal.

The team then analyzed the placental tissue and found that female placentas had coordinated networks of development. That is, when deprived of nutrients, certain genes were up-regulated or down-regulated in a coordinated fashion which adjusted for the deficiencies. In the male placentas, however, they found that this coordination did not occur at the same level. When there were fewer nutrients, the male placentas did not adapt to the lower energy conditions and continued to try to develop all systems.

These differences, the first of their kind reported, suggest a reason why the survival rate of female offspring is greater than that of males. For a primate species to survive, more females are required than males. By adjusting for a less-than-ideal environment while in utero, the female offspring may be preparing for a suboptimal environment once born, and therefore has a survival advantage.

Dr. Laura Cox

Cox and her team are taking these studies a step further by adjusting for specific amino acid deficiencies. Does adding one particular amino acid make a difference? In situations of nutrient deficiency, if one simple change has a significant impact, a supplement may be sufficient to improve maternal and neonatal outcomes.

HIV VACCINE STUDIES

As HIV infection continues to be a global health threat, there is still no cure and no vaccine. Texas Biomed scientists have taken a novel approach in developing an HIV vaccine. Dr. Ruth Ruprecht, Director of the Texas Biomed AIDS Research Program, says this particular vaccine focuses on stopping transmission of HIV at the mucosal barrier.

According to Ruprecht, 90 percent of all new HIV infections occur through mucosal exposure. However, there are individuals who, despite repeated exposure to HIV, do not become infected with the virus. This "natural immunity" is due to the presence of antibodies in their mucosal secretions, specifically IgA antibodies against the HIV gp41 envelope protein. A vaccine that could mimic this natural immunity and therefore prevent infection in other individuals would have a significant impact on transmission rates.

Until now, researchers traditionally have focused on creating a vaccine that elicits specific blood antibodies or cytotoxic T cells, but neither approach has been very successful to date. This new vaccine has been engineered to stop HIV from crossing the mucosal barrier, the initial point of infection. "The Mymetics HIV vaccine candidate uses building blocks from a special part of the HIV envelope protein, called gp41," Ruprecht said.

Ruprecht's team at Texas Biomed has built upon an earlier study in China that used a two-component vaccine protecting all monkeys tested against repeated HIV exposures. Ruprecht and her colleagues have taken this further by testing just one component of the vaccine at a time. They found that to be successful, an HIV vaccine must mount both a mucosal and systemic antibody response to the virus.

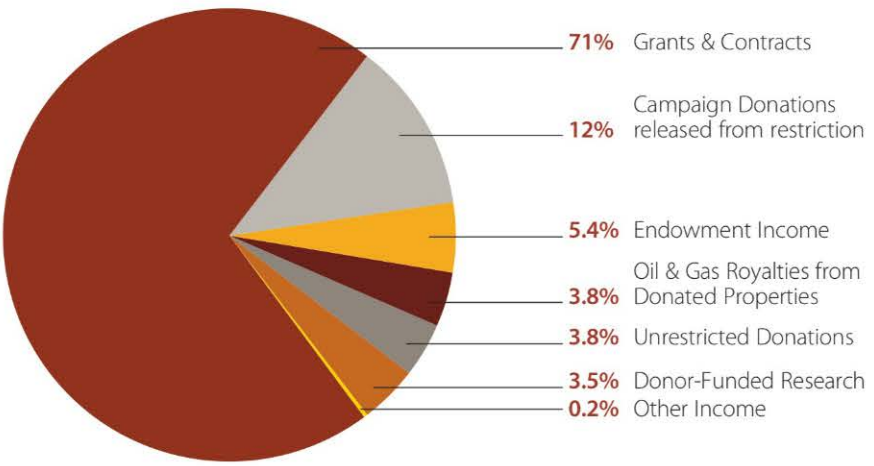
This strategy is called "defense-in-depth" — an approach to defend a vital core by pre-planned, well-armed, multiple lines of defense that can provide backup in case the frontline is breached. When HIV-1 encounters mucosal antibodies generated by the vaccine, those virions will be captured and blocked from crossing the mucosal barrier. However, some virions will remain free, penetrating the barrier. When they do, the second "host defense" will be the systemic antibodies generated as additional immune responses by the vaccine, which can then stop the remaining HIV-1 virions from spreading, preventing systemic infection.

Dr. Ruth Ruprecht

These studies, funded by the Bill & Melinda Gates Foundation, are bringing Texas Biomed and the world one step closer to developing an effective vaccine against HIV infection.

2014 FINANCIALS

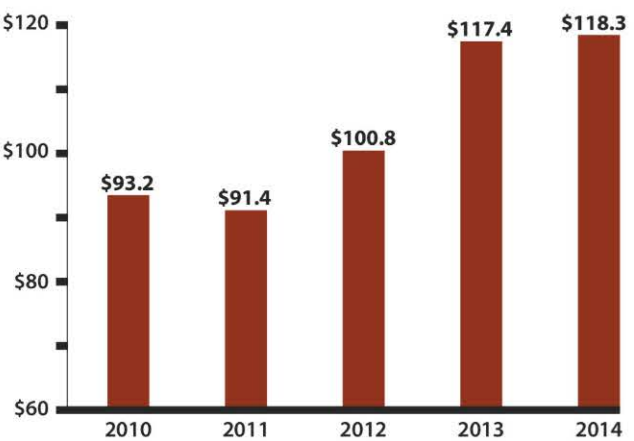
2014 Revenue*



* Based on 2014 Audited Financials

2014 Value of Endowment

In Millions of Dollars



AWARDED IN 2014

GRANTS & CONTRACTS AWARDED

FEDERAL RESEARCH GRANTS AND CONTRACTS

	PRINCIPAL INVESTIGATOR	LENGTH	TOTAL AMOUNT TO TEXAS BIOMED
National Institutes of Health *Southwest National Primate Research Center*	***Dr. Robert Gracy***	*2 years*	*$ 14,809,244*
National Institutes of Health *Genetic Epidemiology of Ocular Health and Disease*	***Dr. Matthew Johnson***	*5 years*	*$ 4,003,099*
National Institutes of Health/Battelle National Biodefense Institute *Efficacy Testing of Filovirus Vaccines in Nonhuman Primates*	***Dr. Ricardo Carrion, Jr.*** ***Dr. Anthony Griffiths*** ***Dr. Jean L. Patterson***	*2 years*	*$ 3,215,169*
National Institutes of Health *Functional Characterization of Regulatory Sequence Variants in Complex Diseases*	***Dr. Michael Olivier***	*4 years*	*$ 2,693,124*
National Institutes of Health *Single Cell Genomics for Malaria Parasites*	***Dr. Ian H. Cheeseman***	*4 years*	*$ 2,287,500*
National Institutes of Health/University of California - San Francisco *Development of a Pedigreed Baboon Genome Resource for Biomedical Research*	***Dr. Laura A. Cox***	*4 years*	*$ 1,805,974*
National Institutes of Health *Establishment of a SPF Rhesus Macaque Colony, Supplement*	***Dr. Robert E. Lanford***	*1 year*	*$ 1,667,796*
National Institutes of Health/Bavarian Nordic A/S *Development of Technologies that Accelerate the Immune Response to Biodefense Vaccines, Supplement*	***Dr. Jean L. Patterson,*** ***Dr. Ricardo Carrion, Jr.***	*1 year*	*$ 1,045,323*
National Institutes of Health *Southwest National Primate Research Center, Supplement*	***Dr. Robert Gracy***	*1 year*	*$ 694,579*
National Institutes of Health/University of Wyoming *Mechanisms of Placental, Fetal Brain and Renal Outcomes of IUGR (Core C)*	***Dr. Laura A. Cox***	*5 years*	*$ 589,073*
National Institutes of Health *Do Early Maternal Antibodies Facilitate Oral Transmission of HIV in Infants? Supplement*	***Dr. Ruth M. Ruprecht***	*2 years*	*$ 551,985*
National Institutes of Health/University of Wyoming *Mechanisms of Placental, Fetal Brain and Renal Outcomes of IUGR (Core B)*	***Dr. Laura A. Cox***	*5 years*	*$ 432,376*
National Institutes of Health/University of Louisville *Development of New Bivalent Cross-Protective Arenaviral Vaccines*	***Dr. Ricardo Carrion, Jr.***	*1 year*	*$ 260,767*
National Institutes of Health/Luminex Corporation *Systems for Rapid Development of High Sensitivity Multiplex Assays for Biothreat Agents*	***Dr. Robert Davey***	*2 months*	*$ 165,494*

FEDERAL RESEARCH GRANTS AND CONTRACTS

	PRINCIPAL INVESTIGATOR	LENGTH	TOTAL AMOUNT TO TEXAS BIOMED
National Institutes of Health/Bavarian Nordic A/S			
Development of Technologies that Accelerate the Immune Response to Biodefense Vaccines	***Dr. Jean L. Patterson Dr. Ricardo Carrion, Jr.***	*1 year*	$ *150,897*
National Institutes of Health/University of Texas Health Science Center San Antonio			
A Novel Mouse Model of Obesity in Pregnancy	***Dr. Laura A. Cox***	*6 months*	$ *109,212*
Total for Federal Research Grants and Contracts under $100,000			$ *291,127*
TOTAL FEDERAL RESEARCH GRANTS AND CONTRACTS			**$ 34,772,739**

PHILANTHROPIC RESEARCH GRANTS

	PRINCIPAL INVESTIGATOR	LENGTH	TOTAL AMOUNT TO TEXAS BIOMED
Bill & Melinda Gates Foundation			
Confirming the Efficacy of Virosomes Targeting HIV-1 gp41 in Indian Rhesus Macaques	***Dr. Ruth M. Ruprecht***	*2 years*	$ *1,854,358*
Robert J. Kleberg Jr. & Helen C. Kleberg Foundation			
Recruitment Package	***Dr. Marcel Daadi***	*3 years*	$ *1,000,000*
Robert J. Kleberg Jr. & Helen C. Kleberg Foundation			
Recruitment Package	***Dr. Tiziano Barberi***	*3 years*	$ *1,000,000*
William & Ella Owens Medical Research Foundation			
Early Indicators of High Osteoarthritis Risk: The Road to Improved Patient Outcomes	***Dr. Lorena M. Havill***	*1 year*	$ *149,816*
Total for Philanthropic Grants and Contracts under $100,000			$ *1,384,161*
TOTAL PHILANTHROPIC RESEARCH GRANTS			**$ 5,388,335**

COMMERICIAL RESEARCH GRANTS AND CONTRACTS

	PRINCIPAL INVESTIGATOR	LENGTH	TOTAL AMOUNT TO TEXAS BIOMED
Bavarian Nordic A/S			
Immunogenicity and Protective Efficacy of MVA-BN-Filo in an Ebola and a Marburg Challenge Model in Cynomolgus Monkeys, Supplement	***Dr. Jean L. Patterson, Dr. Ricardo Carrion, Jr.***	*3 months*	$ *290,136*
AMIORU LLC			
AMIO Antibody Production	***Dr. Robert Davey***	*1 year*	$ *207,791*
Novavax, Inc.			
Immunogenicity of Balb/c Immunized Mice Challenged with Ebola Mayinga, Supplement	***Dr. Ricardo Carrion, Jr.***	*1 year*	$ *197,513*
Arrowhead Research Corporation			
Antiviral Efficacy of RNAi in Chronic HBV Infection #3, Supplement	***Dr. Robert E. Lanford***	*1 year*	$ *144,589*
Total for Commercial Grants and Contracts under $100,000			$ *260,669*
TOTAL COMMERCIAL RESEARCH GRANTS AND CONTRACTS			**$ 1,100,698**
TOTAL MISCELLANEOUS RESEARCH GRANTS AND CONTRACTS			**$ 196,223**
TOTAL GRANTS AND CONTRACTS AWARDED TO TEXAS BIOMED IN 2014			**$ 41,457,995**

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WITH OUR HEARTS FULL AND OUR MINDS SET TO DISCOVER WE THANK OUR DONORS.

While the Texas Biomed team concentrates each day on realizing our mission to enhance lives through discovery, our donors and supporters remind us of why and for whom we strive for such breakthroughs. Donors from across the globe are investing in the ideas and innovations of our team. From the support of groundbreaking pilot studies to new equipment and laboratory space to the recruitment of individual scientists, our donors understand that the support they provide is critical to the future of human health, and for that, we are very grateful.

"WORDS FROM OUR **CHAMPIONS...**"

We have been supporters of Texas Biomed with our time, resources, and advocacy for more than 50 years dating back to the days of seeing Tom Slick's vision grow into reality. We have enjoyed encouraging others to join us through our co-founding roles in the development of both the Forum and Founder's Council. We are assured that our investments and love for the amazing research at Texas Biomed will live on to enhance the lives of us all into the future. ***— Jim and Tena Gorman***

Giving to Texas Biomed has become a multi-generational affair in our family. We give to Texas Biomed because of their good work and the real-life impact this research has had locally and globally. ***— J.J. and Tracee Feik***

As San Antonio natives, we have long known of the brilliant foundations originally envisioned and endowed by Tom Slick Jr. Our focus and fascination has been with one of his most prescient visions, Texas Biomed, for their leading edge research and efforts to understand and find answers to the mysteries of human health and well-being. Fortunately, we've had the added benefit to come to know and count each and every gifted researcher as an admired friend. Our family joins us — as do many of our friends — in following and supporting San Antonio's great treasure, Texas Biomed. ***— Cappy and Suzy Lawton***

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> These funds are provided to Texas Biomed scientists as "seed" monies to initiate new pilot projects that could eventually turn into larger-scale research studies with greater funding.

The Texas Biomedical Forum is a non-profit group of more than 360 women from throughout San Antonio who serve as ambassadors for Texas Biomed in the community. Established in 1971, the Forum was developed specifically to support Texas Biomed through community relations, volunteer services and fundraising.

Each year, the Forum invites high school students from across the city to participate in tours of Texas Biomed. More than 200 students participated in these tours in 2014. Students learned about the many exciting discoveries happening at the Institute and the opportunities to further their own learning and a possible career in science.

The Forum also provides opportunities for its members and friends to learn directly from the scientists at Texas Biomed, as well as outside health experts, on issues relative to diseases being studied at the Institute. These activities started with a roundtable discussion in January followed by lecture luncheons in March and November of 2014 by Texas Biomed Scientist Dr. Ruth Ruprecht and Board Certified Pediatrician and Health Consultant Julie La Barba, M.D., FAAP.

During the spring lecture luncheon, the Forum also celebrated its 20th Annual Science and Education Awards organized by Jody Lutz and Sara McCamish in conjunction with the generosity and dedication of Valerie Guenther and the V.H. McNutt Memorial Foundation. Cash awards totaling $20,000 were given to area high school teachers whose innovative project proposals showed a significant commitment to science education in our community. The LD Ormsby Foundation also supports the science awards by funding a stipend to all applicants.

The Forum's annual gala is a premiere event in San Antonio and is the foundation of the group's fundraising efforts each year. In March 2014, the Forum hosted its Spring Fashion Show at Neiman Marcus in advance of the gala festivities. Guests enjoyed a runway show featuring evening gowns for spring with all proceeds benefitting the Forum's fundraising efforts.

The 2014 "La Dolce Vita" Gala was held May 3rd chaired by Daniella Serna and co-chaired by Ashley Hixon. Nearly 600 guests enjoyed on another sold-out evening of festivities raising $300,000.

These funds are provided to Texas Biomed scientists as "seed" monies to initiate new pilot projects that could eventually turn into larger-scale research studies with greater funding. A list of this year's recipients and their research can be found on page 28 of this report.

(Pictured from L to R) Jordan Arriaga, 2014 Gala Assistant; Daniela Serna, 2014 Gala Chair; Ashley Hixon, 2014 Gala Co-chair.

In October 2014, the Forum kicked off its new year of activities with another great fashion show, "The Best of Fall" fashion show and luncheon at Julian Gold. A portion of the proceeds from that event benefited the 2015 Gala.

The Forum closed out its 2014 activities with a November luncheon honoring past Presidents of the Forum at the home of Karen Lee Zachry. It is through the vision of our founding President and members and the continued enthusiasm and dedication of our current membership and leadership that we are able to provide Texas Biomed with passionate volunteers and critical funds necessary to support research that saves lives.

Sincerely,

Melissa Morgan

Melissa Morgan
2014 Forum President

The Forum awarded nearly $316,000 *in grants to scientists at Texas Biomedical Research Institute to assist in developing preliminary data that will enable these scientists to secure future funding for projects. The following projects were funded in 2014.*

Manu Anantpadma, Ph.D. *Virology & Immunology Dept.*	*Novel macropinocytosis inhibitors as broad spectrum anti-filovirals*
Tim Anderson, Ph.D. *Genetics Dept.*	*Genomic Analysis of Schistosome Hybridization*
Yasuteru Sakurai, Ph.D. *Virology & Immunology Dept.*	*Characterization of the Role of an Endosomal Calcium Channel TPC2 in Ebola virus Infection*
Andrew Hayhurst, Ph.D. *Virology & Immunology Dept.*	*Mapping and modulating specificity of a partially cross-reactive Ebola virus nanobody*
Melanie Carless, Ph.D. *Genetics Dept.*	*Development of a Rapid Screening Technology for the Identification of miRNA-mRNA Interactions*
Frederic Chevalier, Ph.D & Winka Le Clec'h, Ph.D *Genetics Dept.*	*The Microbiome of the Schistosome Snail Host*
Luis Giavedoni, Ph.D. *Virology & Immunology Dept.*	*Understanding natural resistance of baboons against SIV to assist development of new anti-HIV treatments*
Ruth Ruprecht, M.D., Ph.D. *Virology & Immunology Dept.*	*Novel Molecular Strategy to Target AIDS Vaccines to Lymph Nodes Draining Mucosal Barriers*

FOUNDER'S **COUNCIL**

The Founder's Council is a dynamic group of individuals between the ages of 25 and 46 with the goal of building awareness among our city's young talent and creating long-term philanthropic supporters for Texas Biomed.

The Founder's Council was established in 1988 and now boasts more than 330 members from across San Antonio. Members' annual donations help fund competitive grants to Texas Biomed scientists, and their outreach in the community is of great value as we seek to encourage more young professionals to become advocates for scientific research.

> "The activities and fundraising support enables Texas Biomed to make a global impact.

In 2014, the Founder's Council was able to give Texas Biomed nearly $73,000 to fund competitive grants to researchers for the purchase of key pieces of scientific equipment, as well as unrestricted gifts from our higher-level members.

The Founder's Council kicked off the year in February 2014 with a lecture luncheon featuring Scientist Dr. Ruth Ruprecht discussing whether antibodies against the AIDS virus are "Good Guys or Bad Guys." Lecture luncheons are an opportunity for members and their friends to learn more about Texas Biomed's research and scientists. A second lecture luncheon was held in September featuring the Department of Genetics Chair and Scientist Dr. Michael Olivier. His topic was "Can You Hear Me Now? Exciting New Discoveries on Hearing Loss."

In March 2014, members enjoyed the premiere event, Dining and Discourse, where scientists from across all areas of research joined a table of 10 to discuss their science with an intimate group of members.

Throughout the year, we held several networking events for members and prospective members, and our major donors who support the Founder's Council at a level of $500 and above enjoyed an "Epicurean Experience" at The Argyle. Members enjoyed socializing while having each course of a seated dinner paired with a wine.

At the Tobin Estate holiday party, we were honored to present the scientists with their equipment grant awards for the year.

The Founder's Council exists to allow members the opportunity to meet and learn from the scientists, share what they've learned in the community and then support these scientific discoveries financially. The activities and fundraising support enables our members to play a vital role in helping Texas Biomed make a global impact, and we are proud to carry on this great tradition.

Sincerely yours,

Charley Hollimon

Charley Hollimon
2014 President, Founder's Council

FOUNDER'S **COUNCIL**

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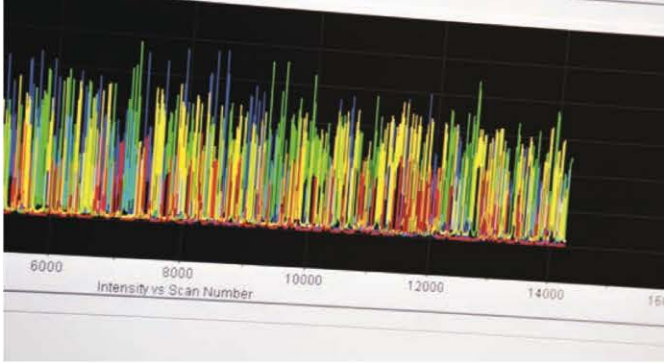

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THE ARGYLE

For more than 50 years, The Argyle, a historic Southern mansion and unique private club, has been devoted to supporting the life-saving efforts of Texas Biomedical Research Institute. The more than 1,500 member club serves as a bond between one of the country's leading independent research institutions and those who give time and money to support it.

Originally built in 1854 as the headquarters of a horse ranch, the mansion was an outpost of Texas hospitality. In 1954, Dr. Harold Vagtborg, the Institute's first president, and Betty Slick Moorman, sister of founder Tom Slick Jr., discussed ways to interest more people in Texas Biomed's work and to create a broader and more permanent base of support for its research programs. Betty Moorman suggested the establishment of a high-caliber club, the members of which would make an annual contribution to Texas Biomed, and thus The Argyle of today was formed.

Under the leadership of Michael Vlad, The Argyle underwent many changes in 2014. From personnel to facilities to member services, Vlad has transformed much of The Argyle's offerings.

The Argyle underwent a redesign of the main alcove, the Hunt room, bar areas and several of the living quarters.

One of the biggest changes in 2014 was the hiring of Justin Keegan as the new Executive Chef. Keegan joined The Argyle from the St. Petersburg Yacht Club in Florida. He spent time in France working with internationally acclaimed chefs and spent six years at the Augusta Country Club in Georgia.

In an effort to provide even more to its members, The Argyle increased musical entertainment and purchased a new Japanese Kawai piano with the help of Mr. John Oberman. The Argyle also refurbished the 1929 Steinway piano thanks to the generosity of Mr. and Mrs. Jim Gorman.

Members were treated to "Special Nights at the Argyle" last year, featuring popular and unique fare. These were a nice addition to one of the most popular initiatives of The Argyle called "Fireside Chats." This program allows members and their guests to meet with Texas Biomed scientists and others in a social setting to enjoy a conversational exchange of ideas, including the opportunity for questions and answers regarding the scientists' research. The Argyle members enjoyed six of these chats in 2014.

Dr. Shelley Cole, Staff Scientist in Genetics, kicked off the 2014 talks in January discussing her work on The Strong Heart Study, a research project on the genetics of cardiovascular disease in Native Americans.

In February, Dr. Anthony Griffiths, Scientist in Virology and Immunology, talked about the work on vaccine development for filoviruses, such as Ebola virus disease.

John Kerr gave a special presentation about the history of The Argyle in April.

After a summer break, Chair of Texas Biomed's Virology and Immunology Department Dr. Jean Patterson and Scientist Dr. Robert Davey discussed life in the BSL-4 laboratory, which allows Texas Biomed to research some of the world's deadliest pathogens.

Dr. Mike Proffitt, Staff Scientist in Genetics, spoke on the future of genetics in October, and we closed out the year in November with a discussion on the promise of stem cell therapy in Parkinson's Disease and other neurodegenerative disorders with one of Texas Biomed's newest scientist Dr. Marcel Daadi.

The Fireside Chats continued to draw greater crowds and enthusiasm throughout the year and will continue into 2015.

Vlad said he looks forward to making additional renovations in 2015 to enhance the member experience, specifically remodeling the kitchen and elevator modernization.

"The benefits of a kitchen remodel will include food delivery time being reduced, increased menu versatility and high-volume production," Vlad said. "Other improvements include the addition of a second access to the main dining room to increase the speed of service."

He said his primary focus in the coming years will be to continue to improve member satisfaction.

"Our vision for an extraordinary club is providing the best quality and services while offering the best value," Vlad added. "Our membership, staff and the vision that was created over 56 years ago has lasted the test of time. We have created a social club where members can entertain themselves, while financial contributions benefit medical research and give humanity hope and prosperity."

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Patrice Frost, D.V.M.

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Michael Owston, D.V.M.

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Shannan Hall-Ursone, D.V.M.

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Cover photo of Dr. Jean Patterson in suit room and p. 18 Dr. Ruth Ruprecht

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