



TEXAS BIOMEDICAL
RESEARCH INSTITUTE

FALL 2011

PROGRESS

Enhancing lives through discovery™



A link is discovered.

Researchers identify specific gene
tied to alcohol abuse.

PAGE 6

INSIDE:

Remembering three Texas
Biomed board members

PAGE 10

LETTER FROM THE CHIEF SCIENTIFIC OFFICER

THIS PAST AUGUST, I HAD THE PRIVILEGE OF SPENDING SOME TIME WITH BORIS LAPIN, M.D., DIRECTOR OF THE INSTITUTE OF MEDICAL PRIMATOLOGY IN SOCHI, RUSSIA, DURING AN INTERNATIONAL CONFERENCE TITLED FUNDAMENTAL AND APPLIED PROBLEMS OF MEDICAL PRIMATOLOGY. THE MEETING WAS HELD IN CONJUNCTION WITH LAPIN'S 90TH BIRTHDAY CELEBRATION. I THINK OF LAPIN AS "THE FATHER OF PRIMATE RESEARCH CENTERS," SO THIS EVENT WAS AN OPPORTUNITY TO RECOGNIZE THE ACCOMPLISHMENTS OF ALL PRIMATE RESEARCH CENTERS AND TO APPRECIATE WHY THEY CONTINUE TO BE A PRECIOUS WORLD RESOURCE.

In this letter, I briefly discuss the history of primate research centers from the first – headed by Lapin – to our Southwest National Primate Research Center (SNPRC), which the National Institutes of Health (NIH) designated in 1999.

Lapin, one of the world's most renowned primatologists, has had an enormous impact on the development of primate research centers worldwide. He made outstanding contributions to many fields of medical primatology at the Sukhumi Primate Center, in Georgia, which was established in 1927. He was instrumental in the field of oncovirology – demonstrating the role of viruses in causing malignant tumors. In 1958, he became head of the Sukhumi center, which developed the world's first pedigreed baboon colony. All 12 Soviet monkeys sent into space were trained under Lapin's direction at Sukhumi.

Why is Lapin so important to U.S. primate research? In 1956 James Watt, M.D., director of the NIH's National Heart Institute, Paul Dudley White, M.D., a

physician of President Dwight Eisenhower, and several U.S. congressmen spent a week with Lapin in Sukhumi. "They were very impressed with our facility and with the research," Lapin recalled. "And they returned . . . and suggested construction of such a facility in the U.S." This visit resulted in the establishment by NIH of the National Primate Research Centers.

In the years since that 1956 visit, many American primatologists have trained at Sukhumi and Lapin has visited many U.S. centers, including our institution in 1963. That visit was his first to the U.S. and the first of four to the SNPRC.

The eight U.S.-designated national primate research centers and other primate research centers worldwide have produced many medical advances. These range from identifying the effects of second-hand smoke on fetuses and newborns, to the development of new pharmacological approaches for Parkinson's disease and drug addiction, to improved methods of

"BORIS LAPIN, ONE OF THE WORLD'S MOST RENOWNED PRIMATOLOGISTS, HAS HAD AN ENORMOUS IMPACT ON THE DEVELOPMENT OF PRIMATE RESEARCH CENTERS WORLDWIDE. HE MADE *outstanding contributions to many fields of medical primatology.*"





Boris Lapin, M.D., in his office at the Institute of Medical Primatology in Sochi, Russia.

in vitro fertilization. The SNPRC has made critical advances in the development of the vaccines for hepatitis A and B and the high-frequency ventilator to rescue premature babies from death or lifelong disabilities.

Lapin's contributions have been unwavering. His research almost didn't survive the early 1990s, when several Balkan states split off from Russia and a civil war erupted in Georgia. By the end of the war, several thousand of Lapin's monkeys were dead or unaccounted for and 90 percent of the primate center facilities were destroyed. Lapin, his scientist wife and four co-workers escaped to Sochi, Russia, which, like Sukhumi, is located on the coast of the Black Sea. Together, they built the new Institute of Medical Primatology from scratch.

Today, Lapin's and other primate research centers are focusing on conquering AIDS and the uncharted territories of emerging infectious diseases. Many have strong research programs in genetics and the relatively new

SNAPSHOT:

Name: Boris Lapin, M.D.

Most Recent Position: Director of the Institute of Medical Primatology in Sochi, Russia

Background:

- Considered the "father of primate research centers," Lapin was instrumental in the field of oncovirology.
- In 1958, he became head of the Sukhumi center, which developed the world's first pedigreed baboon colony.
- All 12 Soviet monkeys sent into space were trained under Lapin's direction at Sukhumi.

Currently:

- Lapin is focusing on conquering AIDS, the uncharted territories of emerging infectious diseases.
- Lapin's institute is now studying monkey physiology in preparation for space flights to Mars.

field of stem cell regenerative medicine, which promises to someday produce technologies for overcoming a wide range of human disorders. Lapin's institute is now studying monkey

physiology in preparation for space flights to Mars.

Lapin said he was eager to host a visit by Russian President Dmitry Medvedev at Sochi to explain the importance of government funding for primate research.

While Lapin plans to leave the director's position this year, he will continue as the center's scientific leader, and his work and legacy live on. The world's primate research centers have a track record of life-saving achievements in the 84 years since the founding of the Sukhumi Primate Center. And they have laid a strong foundation for an escalating pace of medical advances that will benefit people everywhere in this century.

John L. Vandenberg
JOHN L. VANDEBERG, PH.D.

Today, Lapin's and other primate research centers are focusing on **conquering AIDS and the uncharted territories of emerging infectious diseases.**



Texas Biomed Studies will Someday Save Lives of Those who Work with Primates

A FEW YEARS AGO, A RESEARCH ASSISTANT WAS SPLASHED IN THE EYE WITH FLUID FROM A MACAQUE MONKEY. WITHIN SIX WEEKS, EVEN WITH ANTIVIRAL THERAPY, THE WOMAN WAS DEAD. WHY? THE MACAQUE MONKEY CARRIED THE DEADLY HERPES B VIRUS IN ITS SYSTEM AND TRANSMITTED IT TO THE TECHNICIAN THROUGH THIS UNUSUAL ACCIDENT.

Herpes B virus (BV) naturally infects macaque monkeys and is the monkey version of herpes simplex virus (HSV), the cause of cold sores in humans. This virus and HSV are genetically very similar. In the monkey, BV causes self-limiting lesions similar to cold sores. In contrast, human infection with BV is frequently fatal — 80 percent fatality if untreated, 20 percent if treated early. Given that BV is endemic in most macaque colonies, and macaques are the most commonly used nonhuman primate in biomedical research, animal care staff and veterinarians are at great risk of BV infection.

At Texas Biomed, the laboratory of Anthony Griffiths, Ph.D., is working to understand the molecular basis of human disease caused by BV and to develop vaccines that will prevent monkeys from becoming infected with the virus. These studies will lead to the increased safety of those working with these animals. Moreover, they will further the understanding of how highly pathogenic viruses cross between species, which may have implications for developing new treatments for a wide range of diseases, including HSV.

Using the latest sequencing technology, known as deep gene sequencing, Griffiths and his team, particularly



**MACAQUE
MONKEY**
the most
commonly
used
nonhuman
primate in
biomedical
research

graduate student Melanie Amen, have recently discovered 12 BV-encoded microRNAs and are investigating how they regulate the expression of virus and cellular genes. Some of this work has been published in the *Journal of Virology*. "Our studies of microRNAs are furthering our understanding of how viruses successfully infect cells. Ultimately, we anticipate that by comparing the interactions of the virus between human cells and monkey cells, we will gain valuable insight into why the virus is so harmful to humans," says Griffiths.

MicroRNAs are newly recognized molecules that control the expression of genes. They have been shown to be important in many biological processes, and also diseases including cancer. Recently, microRNAs have been shown to be exploited by some viruses, and appear to play fundamental roles in the disease process.

Griffiths' study is the first to combine detailed herpesvirus microRNA identification and expression in the naturally infected host — macaque monkeys — and normally infected cells. The work is so dangerous to humans that many of the experiments must take place in Texas Biomed's biosafety level 4 containment laboratory.

Herpesviruses cause diseases for which there are limited treatments, but no cure. Indeed, as the saying goes, herpes is forever. These viruses have a

two-phase life cycle; they may be actively replicating (when one may see lesions) or "latent," when there is no active replication and almost no gene expression. BV-encoded microRNAs are generated during both phases of the virus life cycle, and are even packaged into the virus particle. And by using the deep sequencing data, Griffiths and his team have developed tests that sensitively and specifically detect the viral microRNAs in infected cells during active replication and latency. These tests have enabled a quantitative analysis of expression throughout the viral life cycles.

The deep sequencing was funded by the Texas Biomedical Forum. Parts of the analyses that have relevance to diagnostic assays were funded by a supplement to the Southwest National Primate Research Center base grant and a National Institutes of Health grant.

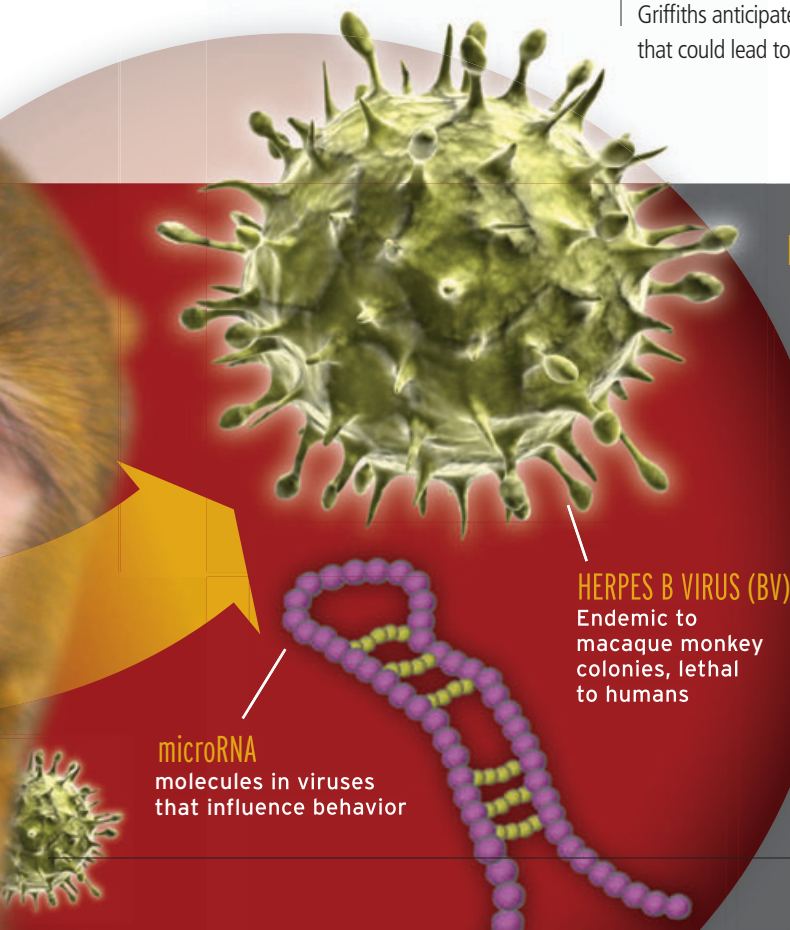
The next steps in this research are to understand how the microRNAs function to facilitate efficient virus replication and latency, and to investigate whether they function differently in human versus monkey cells.

While most HSV infections are self-limiting and fairly minor, HSV can cause serious disease including encephalitis and blindness. Furthermore, HSV causes serious diseases in immunocompromised patients, such as cancer patients receiving chemotherapy, and transplant recipients receiving immunosuppressants. By studying a closely related virus in its natural host, Griffiths anticipates his team will gain valuable insights that could lead to new therapies for HSV. ■



"ULTIMATELY, WE ANTICIPATE THAT BY COMPARING THE INTERACTIONS OF THE VIRUS BETWEEN HUMAN CELLS AND MONKEY CELLS, WE WILL *gain valuable insight into why the virus is so harmful to humans.*"

— ANTHONY GRIFFITHS, PH.D.



HERPES B VIRUS AND THE MACAQUE MONKEY

- The herpes B virus (BV), left, is endemic in most macaque monkey colonies, but is not fatal to the monkeys. In contrast, BV is typically deadly to humans — 80 percent fatality if untreated, 20 percent if treated early. Given that macaques are the most commonly used nonhuman primate in biomedical research, animal care staff and veterinarians are at great risk of BV infection.
- Using deep gene sequencing technology, Texas Biomed scientists have recently discovered 12 BV-encoded microRNAs and are investigating how they regulate the expression of virus and cellular genes.
- **microRNAs** are newly recognized molecules that control the expression of genes. They have been shown to be important in many biological processes. Recently, microRNAs have been shown to be exploited by some viruses, and appear to play fundamental roles in the disease process.

microRNA
molecules in viruses
that influence behavior

HERPES B VIRUS (BV)
Endemic to
macaque monkey
colonies, lethal
to humans

RESEARCH NEWS



“WE KNOW THAT THERE ARE *biological components to risk of addiction.*”

— LAURA ALMASY, PH.D.



Specific gene tied to abuse of alcohol

Using a pattern of brain waves associated with risk of alcoholism, Texas Biomed researchers and others have identified a gene linked to serotonin, a chemical messenger that plays a role in depression.

By starting with brain waves measured in people given specific tasks — known as event-related brain oscillations — researchers first identified patterns common to those at risk of alcohol dependence. “These event-related oscillations are measures of brain activity, and have been shown to be different between people with alcoholism and a random person off the street,” said Laura Almasy, Ph.D., a geneticist at Texas Biomed. “But an important point is that they’ve also been shown to be different in children of alcoholics. These differences in brain activity are not a consequence of someone’s drinking. They’re there beforehand.”

The study included 1,064 members of families with multiple generations of alcoholics in California, Connecticut, Indiana, Iowa, Missouri and New York.

Almasy and her Texas Biomed colleague Mark Zlotutro, Ph.D., performed a genome wide scan to find genes associated with those brainwave patterns. They found a strong link with a variation of the serotonin receptor gene known as HTR7. Serotonin has an effect in the brain on mood and sleep, and many antidepressant drugs work by regulating serotonin. It’s also used by the digestive system. Serotonin is altered in alcohol abuse, and some studies have linked alcoholism to

genes involved in transporting serotonin through the brain.

The findings — the latest from the national, multi-center Collaborative Study on the Genetics of Alcoholism — recently were posted online in advance of publication in the *American Journal of Medical Genetics*.

“Some people are uncomfortable with the idea that there’s a genetic component to addiction,” Almasy said. “But we know that there are biological components to risk of addiction, some have to do with how you metabolize alcohol. Some of them have to do with differences in people’s brains that make them more or less susceptible to addiction.

“And we think this difference in brainwave patterns between people at risk and people not at risk is an echo of whatever that underlying biological difference is that makes some people more susceptible than others,” she said.

Almasy said the gene they found might not be the final culprit in alcohol dependence, as scientists begin thinking about treating the disorder. “Alcohol dependence is complex and this is just one piece of a complicated puzzle. Additionally, if the difference is in the receptor,” she said, “it’s not necessarily at the receptor that we have to intervene. Targeting other parts of the same biological pathway, upstream or downstream of the receptor, could also suggest new treatment options.” ■



FINDING THE LINK

1

Scientists in the Collaborative Study on the Genetics of Alcoholism, a nationwide study including researchers at Texas Biomed, have identified a specific brain wave pattern characteristic of people with alcoholism.



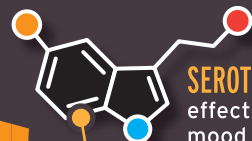
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The same brain wave pattern is seen in children of alcoholics, who are at higher risk of developing alcohol dependence.



3

Texas Biomed scientists performed a genome scan of the subjects with the same wave patterns and found a strong link with a variation of the serotonin receptor gene known as HTR7.



SEROTONIN MOLECULE

SEROTONIN has an effect in the brain on mood and sleep. Serotonin is altered in alcohol abuse, and some studies have linked alcoholism to genes involved in transporting serotonin through the brain.

REMEMBERING THREE TEXAS BIOMED BOARD MEMBERS

CHARLES FOSTER, LOUIS STUMBERG AND HUGH HALFF JR., PROMINENT MEMBERS OF THE TEXAS BIOMED BOARD OF TRUSTEES, PASSED AWAY THIS YEAR.



CHARLES FOSTER

Foster died on July 19 at age 74.

At Texas Biomed, Foster served on the board's executive committee and on several search committees and played a key role in many important decisions. "He was an energetic, capable, no-nonsense leader," said Frank Ledford, M.D., a former Texas Biomed president who was instrumental in introducing Foster to the Institute. "He told me many times that to be on the Texas Biomed board was one of the greatest honors of his life. This is from a man of countless honors."

Foster grew up in Oklahoma City and worked as a carpenter with his father from age 12. He spent three years as an Army paratrooper, serving with the 11th Airborne Division. He attended the University of Oklahoma on the GI Bill, earning a bachelor's degree in engineering. He was a member of four academic national honor societies.

After college, Foster went to work for Southwestern Bell, a small regional phone company. That began a 41-year career in telecommunications, as Southwestern Bell became SBC, and later AT&T. Foster worked in almost every division of the company, including network operations, information systems, international operations, wireless services and merger integration.

He also had a long tradition of philanthropy, joining the board of trustees at the McNay Art Museum soon after arriving in San Antonio in 1993. Foster served on numerous other boards, including Amdocs, an Israeli software company, and Morningside Ministries Foundation. He served as chair of the CPS Energy board during 2010, and helped the utility get back on its feet following a controversial nuclear power deal.

He met his future wife, Carol, on a blind date; they saw "A Farewell to Arms." They had three children.

Foster was also a talented musician, playing bluegrass and country music on the many acoustic guitars he collected.



LOUIS STUMBERG

Stumberg, a food industry pioneer who co-founded the San Antonio company that took frozen Tex-Mex foods nationwide, died on May 3 at age 87.

"Louis had an uncanny ability to reduce complex issues in ways that they could be understood, and played an important role in defining discussions and seeing them through," said Kenneth P. Trevett, Texas Biomed's president and CEO. "His enthusiasm for Texas Biomed's mission and his curiosity about the science remained strong to the end."

Stumberg became Patio Foods Inc.'s president in 1957. The company was acquired by R.J. Reynolds Tobacco Co. in 1967, and Stumberg was named vice chairman of RJR Foods Inc., the company's food and beverage subsidiary.

After retiring in 1986, Stumberg remained very active in government and civic activities. He was a civilian aide to the Secretary of the Army, a Trinity University trustee and a member of the University of Texas at San Antonio Development Board. He served as an elder at First Presbyterian Church; chair of United Way and of the Chamber of Commerce; president of the Boy Scouts and Downtown Rotary Club; and a director of GPM Life Insurance Co.

He was a 1947 graduate of the University of Texas at Austin, and also was known for his hunting expeditions in Africa. Stumberg is survived by his wife of 57 years, the former Mary Patricia Zachry; sons Herb and Eric; a daughter, Diana; three grandchildren; and a great-grandson.

"ALL THREE HAD AN
EXTRAORDINARILY
STRONG BELIEF
IN THE MISSION
OF THIS
ORGANIZATION.
THEY WERE
*very generous
with their
time, counsel
and in many
other ways.*"

— J.R. HURD, TEXAS
BIOMED BOARD CHAIR,
ON CHARLES FOSTER,
LOUIS STUMBERG AND
HUGH HALFF JR



HUGH HALFF JR

San Antonio businessman Halff — a philanthropist, outdoorsman and art collector — died on July 4 at age 76. He led several firms, including WOAI. "He served as a trustee for several years and clearly understood the important role the Institute plays locally, nationally, and outside our country," Hurd said.

A 1953 graduate of the Texas Military Institute, Halff attended Princeton University and then the University of Texas at Austin before returning to San Antonio to go into business.

During his career, he served as CEO of Southland Industries, Blanco Oil, Glastron Boat Co. and Superior Pontiac. He was also CEO of Conroy Inc., which was listed on the American Stock Exchange. He took over WOAI in his early 20s, after his father became ill. His great uncle founded the media company.

Halff served on several boards, including the San Antonio River Authority and the Robert B. Green Hospital. He also sat on art-related committees and boards of the Dallas Museum of Art, the Amon Carter Museum, the San Antonio Museum of Art (SAMA) and the Smithsonian American Art Museum.

The Halff collection of American art has been exhibited at SAMA, the McNay Art Museum and the Smithsonian American Art Museum. He loaned paintings to shows mounted all over the world.

Halff is survived by his wife, Marie Mahone Halff; his son, Hugh Halff III and wife, Dee; his daughter, Stephanie Halff Street and husband, Jerry; two granddaughters, Catherine Ann Street and Ashley Ray Street; and his brother-in-law, Tom Edson.

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Editor: Joseph Carey, Vice President for Public Affairs

Design and production: Ideawire

Photography: Clem Spalding, Larry Walther, John L. Vandenberg, Ph.D.

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IN THE NEWS

Infectious disease specialist joins Texas Biomed

ROBERT DAVEY, PH.D., FORMERLY AN ASSOCIATE PROFESSOR AT THE UNIVERSITY OF TEXAS MEDICAL BRANCH (UTMB) IN GALVESTON, HAS BEEN APPOINTED TO THE POSITION OF SCIENTIST IN THE DEPARTMENT OF VIROLOGY AND IMMUNOLOGY AT TEXAS BIOMED. HE BEGAN AT TEXAS BIOMED ON AUGUST 29.

"We are delighted that Dr. Davey has joined us," said Jean L. Patterson, Ph.D., the department chair. "He is an outstanding researcher and educator, and brings expertise in cell biology, the development of therapeutics and high-containment research."

San Antonio's Ewing Halsell Foundation donated \$2 million to Texas Biomed to fund the new position. "We are very grateful to the Foundation for making this recruitment possible. It is truly a transformational gift," said Kenneth P. Trevett, Texas Biomed's president and CEO. Davey's title is Scientist and Ewing Halsell Scholar.

"The facilities at Texas Biomed are precisely what I need for doing my drug discovery work with high containment viruses," said Davey. "The high containment lab is excellent and the opportunity to work with the trained veterinary staff will be invaluable for helping discoveries move into the clinic."

Davey, 44, a native of Melbourne, Australia, became a U.S. citizen last year. He joined UTMB

SNAPSHOT:

Name: Robert Davey, Ph.D.

Position at Texas Biomed: Scientist in the Department of Virology and Immunology, as of August 29, 2011

Previous Position: associate professor at the University of Texas Medical Branch (UTMB) in Galveston

Specialties: viruses/retroviruses, antiviral drugs

in 2000 from Harvard Medical School in Boston where he was an instructor in medicine. His work focuses on the identification of cellular factors important for establishing infection by retroviruses and more recently, filoviruses, which cause hemorrhagic fever. He is trained to work in biosafety 4 laboratories (BSL4s) and operates a multidiscipline laboratory applying modern molecular techniques to these little-studied pathogens. This has culminated in a deeper understanding of the entry and cell signaling pathways that are used by viruses to penetrate the cell membrane and establish infection.



Davey's work includes discovering and understanding how new antiviral drugs work. Currently, in collaboration with the National Chemical Genomics Center in Bethesda, Md., he is performing a drug screen using 350,000 small molecules to help identify new drugs for prevention and treatment of disease caused by some of the world's most dangerous viruses. This has never been done before on this scale. Texas Biomed will purchase a custom-designed microscope that will let Davey's team watch how viruses move into cells. This approach should enable major discoveries about virus infection and open up new ways to treat disease.

Davey's research has been published in the journals *Nature* and *Science* and, more recently, his work with Ebolavirus has been published in the high-impact journals *PLoS Pathogens* and the *Proceedings of the National Academy of Sciences, USA*.

The Ewing Halsell Foundation is a private charitable trust dedicated to improving the quality of life for Texans by providing access to the arts, education, and quality health care, and by helping provide opportunities for the economically disadvantaged. ■