

PROGRESS

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Meet Larry S. Schlesinger, M.D.

Incoming Texas Biomed President has a vision for growth



TEXAS BIOMEDICAL
RESEARCH INSTITUTE

Enhancing lives through discovery™

Larry S. Schlesinger, M.D.

Researcher, teacher, leader

By Viviane Callier, contributing writer

Incoming president Dr. Larry Schlesinger has devoted his career as a physician-scientist to understanding how the tuberculosis bacterium, *Mycobacterium tuberculosis*, invades and takes up residence in immune cells called macrophages, especially within the lung where initial infection occurs for this airborne bacterium. His work has revealed the molecular machinery for how the tuberculosis bacterium disables the immune system and proliferates inside human macrophages. Once established inside the body, the bug causes latent disease that may progress to a full-blown infection.

More than two billion people worldwide are latently infected with the tuberculosis bacterium, and about 10 million develop a full-blown infection each year, making it the number one bacterial killer in the world. Treatment for tuberculosis typically consists of several months of aggressive antibiotic treatment, but more and more antibiotic-resistant tuberculosis strains are appearing. Furthermore, the bacterium's ability to deactivate the infected patient's immune system makes it very challenging to rid the body of the infection.

Dr. Schlesinger's work has paved the way for the development of host-directed therapies — therapies designed to re-arm the macrophages and bolster the immune system's ability to fight infection. Together with next-generation antibiotics, host-directed therapies promise to be an effective strategy for treating this disease.

Dr. Schlesinger's interest in the biomedical sciences was fostered during his undergraduate days at Cornell University. His current interest in infectious diseases began during his first year at Rutgers Medical School. The physician who led a small group discussion, a specialist in infectious diseases, would present medical cases that were difficult to diagnose. Dr. Schlesinger loved the detective work and deductive reasoning needed to

arrive at a correct diagnosis, a hallmark of this discipline. He became fascinated by these diseases and went on to the University of Michigan, where he received his clinical training in internal medicine and engaged in research.

Following his curiosity, he went to University of California, Los Angeles, to do a clinical and extended research fellowship in infectious diseases with Marcus Horwitz, MD, who became a life-long mentor. After his fellowship, Dr. Schlesinger became a faculty member at University of Iowa, where he conducted research on tuberculosis and continued seeing patients in the clinic. Soon after becoming a full professor, Dr. Schlesinger discovered a new passion: developing robust scientific organizations and working with groups of scientists beyond his own laboratory.

That led him to Ohio State University, where he founded the Center for Microbial Interface Biology, a highly interdisciplinary research institute whose goal was to understand how microbes adapt their physiology when they encounter their host, and in turn change the host's physiology.

"My talent for bringing people together and having them understand how to capitalize on each other's strengths is something that I particularly enjoy doing," Dr. Schlesinger said.

He continued to see patients in the clinic until 2011, when he decided to dedicate himself full time to research and teaching. He became chair of the Department of Microbial Infection and Immunity at Ohio State. In that role, he worked primarily with PhD scientists, as well as physicians, veterinarians, and even pharmacists in training. All told, he has trained more than 170 researchers. In addition to maintaining an active research program in his own laboratory, he was the director of the Medical Scientist Training program at Ohio State, an NIH-funded program to train young physician-scientists.

“That was pure joy for me,” he said.

At this stage in his career, Dr. Schlesinger became acutely aware of the challenges facing biomedical research and the pressures put upon research universities.

“I became intrigued by the opportunity to lead a private, non-profit research institute where the mission is more focused, the operations more flexible, and the resources more varied. This excited me,” he said.

So, he took the leap to Texas Biomed. Texas Biomed has seen its research programs evolve organically over the last 75 years, and the Institute has capitalized on opportunities as they presented themselves.

“But, based on changing forces, this approach isn’t as viable today, and we now need a much more calculated, strategic approach to science,” Dr. Schlesinger explained.

Under his leadership, the Institute will undergo a comprehensive strategic planning process to optimize productivity and synergy across research groups. Dr. Schlesinger also envisions re-organizing workspace to increase interaction and collaboration among researchers within the Institute. Dr. Schlesinger highlighted two unique resources he plans to leverage at Texas Biomed: the Biosafety level 4 (BSL-4) laboratory and the national primate center, which enable researchers to conduct pre-clinical research that would be difficult to conduct anywhere else in the country.

“I believe we can be the number one in the country in bio-containment research,” Dr. Schlesinger said. “And, this opens doors for opportunities with public agencies and private foundations to perform science that is necessary to gain FDA approval for new therapies and vaccines.”

Federal funding for biomedical research has been flat for the last 15 years, so “to be solely dependent on federal funding is a mistake,” Dr. Schlesinger said.

But with support from the community, the Board of Trustees, and a large network of donors, Dr. Schlesinger is confident Texas Biomed’s future is bright. Winning support from private foundations like the Bill and Melinda Gates Foundation, which currently supports part of Dr. Schlesinger’s tuberculosis research, will be part of the strategy.



Dr. Larry Schlesinger (right) and Dr. Eusondia Arnett in their new laboratory at Texas Biomed. Photo/Josh Huskin

“We need to position the institute to capture additional funding streams in the public and private sector to give us a sustainable advantage,” Dr. Schlesinger said.

Texas Biomed is an ideal place for Dr. Schlesinger to move his tuberculosis research program forward. One of the bottlenecks in tuberculosis research is to understand the enormous variation that occurs in the human immune response.

“Those differences in immune response have bearing on how individuals respond to a given therapy or vaccine,” said Dr. Schlesinger. “We need to get a handle on how an individual human might respond to a therapy or vaccine. That is one of the great challenges that I hope to be able to focus on as an institute investigator.”

Drs. Abul Azad and Eusondia Arnett, currently senior members of Dr. Schlesinger’s lab at OSU, have moved to

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Improving the whooping cough vaccine at Southwest National Primate Research Center



Dr. Robert Lanford, Director of the Southwest National Primate Research Center. Photo/Josh Huskin

By Viviane Callier, contributing writer

Pertussis, or whooping cough, has seen an alarming resurgence in the last decade. That's surprising, given that a vaccine for this infectious disease has existed since the 1930s. The original vaccine, made with whole-cell killed *Bordetella pertussis* bacteria, was very effective but associated with some adverse events. A newer acellular pertussis vaccine with fewer adverse events was approved by the FDA in 1997. Recent epidemiological studies have found, however, that the immunity conferred by the new vaccine wears out during adolescence.

That's a problem, because although whooping cough isn't fatal to adults, adults whose immunity has waned

can carry and transmit the disease to infants, for whom it is frequently fatal. Infants typically receive antibodies from their mothers, but if the mother is not immune to pertussis, she cannot pass on immunity to the infant — thus putting the infant at risk of infection. And although the pertussis bacteria can be killed with antibiotics, the toxins released by the bacteria have done irreparable damage to the lung by the time the infant develops whooping cough.

A current but imperfect strategy to protect infants is "cocooning" — that is, vaccinating anyone who might come into contact with the infant, including parents, siblings, grandparents, babysitters, and the like. Nevertheless, the loss of pertussis immunity in the adult

population as a whole, combined with the fact that many parents now choose not to vaccinate their children, has caused pertussis to become one of the largest preventable causes of death due to infectious disease worldwide in infants.

To address this problem, researchers have been working to develop an improved pertussis vaccine. Some of these new strategies are now ready for pre-clinical testing, which is required by the FDA before moving forward with human clinical trials. “It turns out the baboon is the perfect model for pre-clinical testing, because it is the only animal that mimics humans in that infant baboons develop a persistent cough when exposed to pertussis,” explained Dr. Robert Lanford, Director of the Southwest Primate Research Center (SNPRC).

SNPRC is one of seven NIH-funded primate research centers across the country, and the only one that houses a colony of baboons. It is thus in a unique position to advance pertussis vaccine research at this critical stage.

Working with the FDA and pharmaceutical companies, Lanford’s team is using the baboon model for testing new approaches to improving the acellular vaccine. Some

of these new approaches use novel adjuvants (compounds designed to enhance immunity to vaccines) that can be used in combination with the existing acellular pertussis vaccine.

“The fastest way to get a better vaccine is not to make a new vaccine, because it takes decades to get a new vaccine approved; it is to enhance one that we already know is safe,” Dr. Lanford said.

Of course, this isn’t guaranteed to work, so some research groups are taking different approaches and attempting to develop a new vaccine from scratch, he added.

The goal is to produce data that will be used by the FDA to evaluate the potential effectiveness of the new vaccine and to decide if it can move forward to testing in human clinical trials, explained Dr. Lanford. It is usually a multi-year process.

“Drugs that look most promising at first can run into safety problems,” Dr. Lanford explained. “It’s hard to predict which one will get through all three phases of human clinical trials — that’s why we need to work on multiple different approaches simultaneously.”

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Texas Biomed to continue their work. Dr. Arnett studies a protein that regulates gene responses to TB infection. Serendipitously, she discovered that this protein is a cell death protein that is highly expressed in some cancer cells.

“We were able to capitalize on that discovery and find a preclinical therapeutic developed to treat cancer that can also limit the growth of the Mycobacteria tuberculosis in macrophages,” she explained.

Dr. Azad has worked in Dr. Schlesinger’s lab for more than a decade and has recently screened a library of small molecules for their ability to kill the tuberculosis bacterium.

“By repurposing drugs developed for cancer treatment, I’ve found several molecules that kill tuberculosis bacteria in vitro,” he explained. “The next step, given enough funding, will be to test these molecules in animal models.”

Dr. Schlesinger plans to capitalize on the nonhuman primate capabilities at Texas Biomed to do pre-clinical work. Nonhuman primates are recognized as the premier animal model for tuberculosis.

“Until now, I have not had such ready access to primates in my research, so that is a tremendous advantage,” he said.

And, in San Antonio is the country’s only free-standing tuberculosis hospital, which treats patients with drug-resistant tuberculosis. Collaborations with the hospital will help bridge the continuum from basic science discovery to the clinic.

“Basic science discoveries can be door-opening discoveries for the clinic, and you don’t want to miss those opportunities,” Dr. Schlesinger explained.

Profile: Dr. Frédéric Chevalier

A cutting-edge geneticist and old-school genealogist

By Viviane Callier, contributing writer

Hailing from Perpignan, a southern French city near the Mediterranean coast and the border with Spain, geneticist Dr. Frédéric Chevalier came to Texas Biomed five years ago to work with Dr. Tim Anderson on schistosomiasis, a tropical disease caused by parasitic worms. The worms parasitize freshwater snails, which then release larvae infective to humans who come in contact with contaminated water. Dr. Chevalier has been working to identify the genes that allow the fluke to survive in the snails. He also wants to understand the genetic diversity in the population of flukes and discern which genes have been the targets of natural selection. “The genes under selection can be good vaccine candidates,” he said.

Dr. Chevalier is a talented evolutionary geneticist and bioinformatician. But when it comes to understanding his own ancestry, Dr. Chevalier prefers to do things the old-fashioned way: by researching documentation of births, deaths and marriages. So far he has traced his ancestry back to the 17th century and has placed more than 1,500 people on his family tree. “That’s just on my mother’s side,” he said. He’s still got his father’s side to do.

Dr. Chevalier’s genealogy project, which he started in 2006 and, after a hiatus, picked up again when he moved to Texas, has helped him reconnect with his roots.

He knew that his family was from the Pyrénées, the mountains that separate Spain from France, and slowly migrated from west to east along these mountains. But he discovered that some of his ancestors come from the Rhône, “a part of France that I didn’t suspect. It wasn’t known from the histories that are kept in the family, so that was totally new to me,” he said. He was also able to trace the stories of his ancestors who lived in Algeria when it was a French colony (1827-1962).

Living in Texas has been a change from his French



*Dr. Frédéric Chevalier in the lab with snail tanks behind him.
Photo/Josh Huskin*

hometown, but Dr. Chevalier has found it a good place to be. The funding situation for science is better here than in France, he says, and he was taken by the friendliness of people in San Antonio. “In France, people complain a lot and it can be annoying sometimes,” he explained. He’s also been pleasantly surprised by the local culinary offerings.

Although he needs no convincing about the power of genetics to fight infectious disease, Dr. Chevalier enjoys the detective work of being a genealogy hobbyist and is adamant that he doesn’t want to get genetic testing. “You learn to read people’s interactions through the documents,” Dr. Chevalier said. “It’s something that the genes will never tell you. If you want to know yourself, it’s better to dig into the documents to understand the human part of your history.”

Evolutionary approach to combatting malarial drug resistance receives millions in NIH funding

Between 2010 and 2015, the world saw a 21 percent decrease in the incidence of malaria and a 29 percent decrease in malaria death rates, according to the World Health Organization's 2016 World Malaria Report.

"Malaria control is currently riding a wave of success, largely on the back of a potent antimalarial called artemisinin," explained Dr. Timothy Anderson, Scientist at Texas Biomed. "This drug is used in a cocktail with one of several other antimalarials, and these combination therapies have been extraordinarily effective in reducing malaria deaths. Unfortunately, the recent emergence of resistance to artemisinin now makes this a critical time for malaria control efforts."

In early 2017, Dr. Anderson received a five-year, \$4.6 million MERIT Award from the National Institutes of Health (grant #4R37AI048071-16) to enable he and his team to expand their efforts to examine resistance evolution in the malaria parasite in Southeast Asia and to apply powerful new gene editing technologies to better understand drug resistance evolution. Malaria still currently infects more than 200 million people worldwide, killing more than 400 thousand annually.

"We can now rapidly add or remove resistance mutations to parasites grown in the laboratory, so we can understand precisely what biochemical pathways are affected," Dr. Anderson said. "These methods will be critical for our understanding of artemisinin resistance. Our aim is to identify the parasite genes that underlie resistance, to determine how frequently resistance arises, to monitor the spread of resistance and then to use this information to help design treatment strategies that can prevent resistance from arising in the first place."

Dr. Anderson's laboratory has made key discoveries concerning artemisinin resistance. Just three years after the emergence of artemisinin resistance was initially

documented, his laboratory identified a small segment of the malaria parasite genome that contained the major resistance gene involved. The speed with which the genetic determinants of resistance were identified makes all the difference for malaria control efforts.

Dr. Anderson said their work uses a rather different approach from classical public health efforts, which focus on finding immediate solutions to reducing malaria deaths but don't always consider longer term ramifications of their treatment efforts.

"You need the Band-Aid approach, but if we are going to develop new drugs, we need to think carefully about what kind of drug combinations we need to prevent resistance from occurring in the first place," Anderson commented.

Artemisinin is currently used in combination with another drug, but Dr. Anderson emphasized that a combination of just two drugs has not prevented resistance from evolving.

"Drug combinations need to be more complicated if we are to prevent resistance from arising. We need to take some lessons from the HIV and TB playbook to stack the odds against drug resistance evolving in malaria," he said.

Dr. Anderson's malaria laboratory currently includes

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*Scientist Dr. Timothy Anderson,
Interim Chair, Department of
Genetics*

Texas Biomed hosts first Strong Heart Study Community Symposium

The Strong Heart Study (SHS), which began in 1988, is the largest epidemiological study of American Indians ever undertaken and aims to study cardiovascular disease and its risk factors among American Indian men and women, according to the National Heart, Lung and Blood Institute (NHLBI) website. Tribes participating in the study hail from an area near Phoenix, Arizona, the southwestern area of Oklahoma, and western and central North and South Dakota.

The SHS Steering Committee, chaired by Texas Biomed Associate Scientist Dr. Shelley Cole, who also leads the SHS Genetics Center, held a Community Symposium in September 2016 on the Texas Biomed campus. It was the first assembly of its kind, bringing together 18 community members from among 12 Strong Heart Study tribes along with representatives from the NHLBI as well as researchers and team members from across SHS research institutions.

"It is important that the Strong Heart Study not only have the participation but the input and guidance from the communities they serve to ensure the study accurately and effectively addresses the major health problems of the communities," said Dr. Cole. "This meeting was a great opportunity to share what each of the study centers have learned, as well as gain input from the community about current and future SHS research projects."



(pictured left) Dr. Lonnie Nelson, Principal Investigator, SHS FITSMU (Family-Based Intervention to Reduce Stroke Risk in Indian Country), Eastern Band Cherokee, University of Washington, talks with attendees during a breakout session at the SHS symposium at Texas Biomed in 2016. Photo/Greg Garrison

In addition to presentations on the history and progress of the SHS, researchers from Texas Biomed presented the latest in research technologies and provided tours of the campus. Scientists from across the SHS centers presented data on individual studies, including Family-Based Intervention to Reduce Stroke Risk in Indian Country: The FITSMU Trial, Understanding the Role of Arsenic in Cardiovascular Disease: Opportunities for Prevention in the Strong Heart Study Communities, the Stop Atherosclerosis in Native Diabetics Study (SANDS) Trial and Rhythm and Timing Exercises to Improve Stroke Risk Outcomes.

"It was important that, as researchers, we listen to the ideas and concerns of the community and share how much we have learned and how far we have to go."

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Shalini Nair, Marina McDew-White, Vinay Menon and Ann Arya. He also collaborates closely with Dr. Ian Cheeseman, now a faculty member at Texas Biomed, who conducted pioneering work that led to the identification of a key artemisinin resistance locus as a

postdoctoral scientist in Dr. Anderson's lab. This research would not be possible without close collaboration with François Nosten, M.D. of the Shoklo Malaria Research Unit, in Thailand, that is part of the Mahidol-Oxford Research Unit (MORU).