A CLOSER LOOK

TOP DISCOVERIES OF THE DECADE

Pulse magazine asked University administrators to look back over the last 10 years and tell us which NJMS discoveries stand out. Here are three huge breakthroughs. **BY MARYANN BRINLEY**

A Transformational TB Test

David Alland, MD, chief, Division of Infectious Disease, designed and developed a revolutionary, diagnostic tuberculosis (TB) test that is fast, cheap and clinically effective anywhere. This can be used in a doctor's office, a clinic or just about everywhere in the world of public healthcare medicine. Alland, who has been working on rapid tests for TB since 1988, led the research, which has performed well in large-scale field trials. The work was done in collaboration with Cepheid, a molecular diagnostic company based in California, and the Foundation for Innovative New Diagnostics (FIND), which designed and supervised the study. Grants from the National Institutes of Health and FIND supported the work which took years for Alland to complete.

In less than two hours, what might look like a harmless cold or cough can be diagnosed as a clear-cut case of TB with the Xpert MTB/RIF test. The World Health Organization (WHO) formally endorsed the test in December, recommending that it be used to replace smear microscopy in HIV-positive patients and those suspected of having multi-drug resistant tuberculosis. The Xpert MTB/RIF is the first test in more than a century to replace the microscope as the primary means for detecting tuberculosis.

Active TB is easy to misdiagnose. Older tests relied on skin, blood cultures or sputum smears. A culture could take from seven days to several months to complete and a correct diagnosis of active TB might also require a complete physical exam, chest X-ray, and looking at the lung using a bronchoscope. Meanwhile, TB spreads easily through the air in droplets expelled through coughing. This 4,000-year-old germ, *Mycobacterium tuberculosis,* is responsible for killing nearly two million people a year. So in this era of regular global travel, multi-drug resistant (MDR) TB strains, and epidemic numbers of HIV immune-compromised individuals who are more susceptible to TB, this fast, inexpensive, portable test had been an urgent public health need. Individuals from Lima, Peru; Baku, Azerbaijan; Cape Town and Durban, South Africa; and Mumbai, India participated in the study, titled "Rapid Molecular Detection of Tuberculosis and Rifampin Resistance," which was published in the September 1, 2010 issue of the *New England Journal of Medicine.* Alland, who is the interim director of the UMDNJ Center for Emerging Pathogens, says, "The test also indicates rapidly whether difficult-to-treat, drug-resistant forms are present."

Gwen Mahon, PhD, director, Office of Research and Sponsored Programs (ORSP), says, "For the first time, this test makes it possible to detect tuberculosis at its point of care, directly from a clinical sputum sample. Dr. Alland's work sets the bar that all future point of care tests for infectious disease will be compared to." Not completely surprised by his success, he admits that there were times along the way that he "didn't think it was going to happen at all." Credit for this new TB test must also go to a long list of collaborators but especially: Danica Helb and Elizabeth Story at UMDNJ; Fred Kramer, Sanjay Tyagi, and Hiyam El-Hajj at the NJMS–Public Health Research Institute (PHRI); Bill McMillan, Martin Jones, David Persing, Emily Windean at Cepheid; Amy Piatek and Michael Levy at Montefiore Medical Center; and Mark Perkins at FIND.

Glucose Sensors in the Brain

Diabetes and obesity are taking a huge toll on health in the developed world. For more than a decade, Vanessa Routh, PhD, Barry Levin, MD, and Joseph McArdle, PhD, have studied the mystery of how the brain senses and responds to the body's metabolism. Routh, professor, pharmacology and physiology, and Levin, professor, neurology and neurosciences, published "The role of the brain in energy balance," in the *American Journal of Physiology* in 1996. In citing this ground-breaking research,

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ORSP Director Mahon also pointed to a study published by Levin, Routh, and McArdle, professor, pharmacology and physiology, in the journal, *Diabetes,* in 2001, that described how specific neurons in a part of the hypothalamus are activated by glucose and another subset of neurons is inhibited by glucose.

"We have only to read the news or look around us to know that obesity and Type 2 diabetes mellitus are serious health issues," says Routh. "In fact, obesity and its co-morbidities (heart disease, hypertension, stroke and cancer) are the second leading cause of death in the U.S." It would be easy to blame lifestyle choices and poor dietary habits alone for this epidemic but Routh and her colleagues have found other factors in the brain. "Most people probably do not suspect that their brain is at fault for their increasing waistline or diabetes, but there is no doubt that the brain plays a major role in regulating energy homeostasis. Moreover, growing evidence indicates that dysfunction in the way that the brain senses nutrients contributes strongly to the development of peripheral insulin resistance." Glucose, a sugar energy source and the most versatile of fuels, is highly preferred by the brain.

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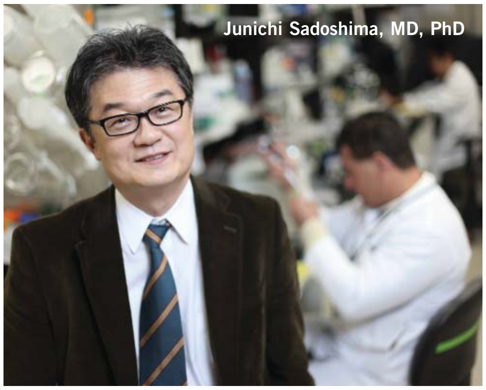
Routh's overall hypothesis is that maintaining energy balance is a critical function of the brain. "We are particularly interested in specialized glucose-sensing neurons that respond to nutrients (glucose, lactate and fatty acids) and hormonal changes. And, we've shown that the glucose sensitivity of these neurons follows changes in peripheral energy status in both health and diabetes. Dr. Zentau Song, a member of our team, and I were the first to characterize glucose-sensing neurons in the presence of glucose concentrations which would be seen in the living brain during normal daily fluctuations, as well as during diabetes," Routh explains.

"My lab studies the neuromuscular junction," explains McArdle. "This synapse is altered in diabetes. Understanding the molecular basis of how diabetes alters this junction will provide insight into the way this disease affects the brain and other aspects of human behavior including eating. Common sense and logic suggest that diabetes alters the supply of energy to snyapses." Yet, McArdle says that it's remarkable that no one has yet determined the energy required to operate or to change a chemical synapse (what is actually happening in learning, for example). He also points out that there is a great deal of other important work being done at NJMS on understanding and preventing diabetes.

Their long-term goal is to understand the cellular mechanisms underlying these sensors and to learn how they become dysfunctional during obesity and diabetes. "For the past 25 years," adds Levin, "we have searched for the biological factors that predispose individuals to become obese and for the underlying reasons why so few can maintain weight loss after they become obese… Our studies have shown that there are genetic, neurological and metabolic causes for this resistance to permanent weight loss." His work has shown that the best time to prevent or ameliorate the development of obesity may be very early in life. "One finding in rodents is that early onset exercise might help prevent the onset of diabetes," Levin says.

New Approach to Heart Failure

Recognized as a world leader in the field of cardiac growth and survival signaling, Junichi Sadoshima, MD, PhD, discovered a novel approach to medical treatment for heart failure. "Heart failure is the number one cause of death in this country and is usually accompanied by enlargement of the heart, which is mediated by a mechanism involving what are called histone deacetylases (HDACs). Our work was the first to show regulation of the function of this HDAC by protein oxidation."



Junichi Sadoshima, MD, PhD

In life, your body constantly interacts with oxygen as you breathe and as cells produce energy. Unfortunately, research has shown that these very natural processes produce highly reactive molecules known as free radicals, which can cause oxidative damage. To counteract this damage, the body manufactures anti-oxidants to defend itself. However, that ability to create anti-oxidants naturally is controlled by genetic makeup and influenced by environmental factors. Sadoshima's research focused on cardiac hypertrophy (heart enlargement) but oxidative damage is implicated in cancer, Alzheimer's, and symptoms of aging.

Collaborating with postdoctoral fellow Tetsuro Ago and assisted by Hong Li, PhD, and Tong Liu, in the proteomic core facility, Sadoshima, who is a professor and executive director, Cardiovascular Institute, explains that the team found a small molecule, thioredoxin 1 (Trx1), that acts like an anti-oxidant and inhibits cardiac enlargement under stressful conditions. This breakthrough research was published in *Cell* and supported by a grant from the NIH and the Fondation Leducq Trans Atlantic Network. Sadoshima started his career in Japan at Kyushu University where he earned both his MD and PhD. After spending time at Harvard Medical School, the University of Michigan and Allegheny University of the Health Sciences in Pittsburgh, he arrived at NJMS in 2000.

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