UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

somnews

October 2015 Vol.17 No.2

DEAN'S MESSAGE: What's On My Mind

What's on my mind this month is the new school year. As we get going again, I am torn between two emotions. On the one hand, I'm proud of all we've accomplished over the summer, and on the other, I'm excited for what we have coming up in the fall and winter.

To begin, I am delighted to welcome a new group of medical students, the Class of 2019. We have 159 students, from more than 5,200 applicants. They come from 67 different colleges and universities, and have an impressive average GPA of 3.76, well above the national average. Welcome, and good luck!


Back-to-school reception with Oriole bird as special guest

Over the summer, our faculty has been involved in a number of impressive projects. In August, two of our researchers were involved in setting up an unprecedented meeting, where a group of disparate and often adversarial civilian and military officials from Myanmar (formerly Burma) created an extraordinary coalition to fight malaria in the region. It was truly a historic meeting, a model for how to use science and medicine to solve major health problems and as a way to foster wider social and political change. The meeting was the result of years of work by **Christopher Plowe, MD, MPH**, Director of our new Institute for Global Health, and **Myaing M. Nyunt, MD, MPH, PhD**, Assistant Professor, Department of Medicine, and Director of the Institute's efforts in Myanmar. They spent countless hours talking and negotiating with all sides, and this hard work led to a global health breakthrough.

In this issue, we are highlighting the exciting range of innovative brain research at the University of Maryland School of Medicine. Scientists from many disciplines are using innovative strategies to solve crucial questions. This work will be the focus of **our third annual Festival of Science in December.** This year we'll have a **new location, the SMC Campus Center**, which will be able to hold a larger audience. We expect several hundred people from our academic community to attend the conference.

Our brain scientists are breaking new ground, uncovering insights that have the potential to improve treatment for patients with a range of ailments, from brain trauma to schizophrenia. **Michael T. Shipley, PhD**, the Donald E. Wilson, MD, MACP, Distinguished Professor and Chair, Department of Anatomy & Neurobiology, is examining a very basic, but very important, question. On a cellular level, how does the brain organize itself? Shipley follows individual neuronal cells as they react to stimuli, and has so far delineated 3,000 neural circuits. Without this kind of fundamental research, translational science would be impossible.

Some scientists are focusing on particular disorders, laying the foundations for potential treatments in the future. **Laura M. Rowland, PhD**, Associate Professor, Department of Psychiatry, is using cutting-edge imaging technology to understand why many patients with schizophrenia have learning and memory problems. **Robert Schwarcz, PhD**, Professor, Department of Psychiatry, also studies schizophrenia. He is focused on a new approach to improving cognition in people with the disease by increasing brain levels of glutamate.

We're also tackling problems that have a particular relevance to our own city and region. **Bankole A. Johnson, DSc, MD, MB, ChB, MPhil, FRCPsych, DFAPA, FACFEI**, the Dr. Irving J. Taylor Professor and Chair, Department of Psychiatry, and Director of the Brain Science Research Consortium, directs the school's new Clinical Neurobehavioral Center, which studies the treatment of alcohol and drug addiction, and is now studying personalized approaches to treat alcoholism. Johnson is also a member of the Heroin and Opioid Emergency Task Force for the state of Maryland, which is in the midst of an epidemic of abuse involving these substances.

There are other members of the consortium doing work that could soon be used by patients. **Graeme Woodworth, MD**, an Associate Professor in the Department of Neurosurgery, is trying new approaches to diagnose and treat brain cancer. He is testing metabolic imaging, an approach that identifies metabolic signatures of tissue, as well as focused ultrasound, a technology that uses sound waves to interact mechanically with tissue. He is part of a multidisciplinary team that includes **Howard M. Eisenberg, MD**, Professor and Chair in the Department of Neurosurgery and **Elias R. Melhem, MD**, Professor of Diagnostic Radiology and Nuclear Medicine and Chair in the Department of Diagnostic Radiology & Nuclear Medicine, who are the principal investigators. Also involved are **Rao P. Gullapalli, PhD, MBA**, Professor of Diagnostic Radiology and Nuclear Medicine, **Dheeraj Ghandi, MBBS**, Professor of Diagnostic Radiology and Nuclear Medicine; **Dirk Mayer, Dr. Rer. Nat.**, Associate Professor of Diagnostic Radiology and Nuclear Medicine; **Joseph P. Kao, PhD**, Professor of Physiology; **Victor Frenkel, PhD**, Associate Professor of Diagnostic Radiology and Nuclear Medicine; **Paul S. Fishman, MD, PhD**, Professor of Neurology; and **Charlene Aldrich, RN, MSN**, from the Neurosurgery Department.

These are just a few of the exciting brain science projects at the school. Together, all of this work will make a difference in how we understand and treat brain disorders in the years to come.

In the relentless pursuit of excellence, I am

Sincerely yours,

E. Albert Reece, MD, PhD, MBA
Vice President for Medical Affairs, University of Maryland
John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine

Point of Pride

Frank C. Ayd, MD, Class of 1945, was granted the first permit from the U.S. Food and Drug Administration to give Thorazine to patients with schizophrenia.

Today, the Maryland Psychiatric Research Center, a division of our Department of Psychiatry, is an internationally recognized leader in schizophrenia research.

This makes us proud!

Preview

Third Annual

FESTIVAL of SCIENCE

BRAIN SCIENCE BREAKTHROUGHS:

From Addiction to Trauma—

The human brain contains more than 200 billion nerve cells, which together form a series of complex networks linked by myriad chemical messengers. Over the past century, scientists have made huge gains in their understanding of how this biological computer works. At the same time, there is still an enormous amount that we have yet to unravel. At the University of Maryland School of Medicine, researchers from many disciplines are using innovative strategies to solve these crucial questions. In this issue, we celebrate some of the basic, translational and clinical work focused on understanding the brain and treating its diseases that will be featured at this year's Festival of Science.

Pain and Addiction

Bankole A. Johnson, DSc, MD, MB, ChB, MPhil, FRCPsych, DFAPA, FACFEI

The Dr. Irving J. Taylor Professor and Chair, Department of Psychiatry and Director of the Brain Science Research Consortium

Professor Johnson, an expert on the use of medication to treat addiction, pioneered the use of two drugs, topiramate, an anti-epileptic, and ondansetron, an anti-emetic, as a treatment for alcohol and cocaine dependence. He directs the school's new Clinical Neurobehavioral Center, which studies the treatment of alcohol and drug addiction, and is now studying personalized approaches to treat alcoholism, as well as the use of topiramate to help people with alcohol problems quit smoking. Professor Johnson was recently appointed as a member of the state of Maryland's Heroin and Opioid Emergency Task Force. The state is in the midst of an epidemic of heroin and opioid abuse.

Asaf Keller, PhD

Professor, Department of Anatomy & Neurobiology

Pain is not only a physical experience, but an emotional one, and people with chronic pain often suffer from depression and anxiety disorders, too. The relationship between pain and emotional distress also works the other way: patients with depression and anxiety often experience pain more strongly. Dr. Keller is studying the neurobiological links between pain and emotion. He and his colleagues are focusing on a brain region called the periaqueductal gray (PAG), which is crucial for the sensation and control of pain. They have discovered that the PAG interacts with another brain region known as the lateral parabrachial nucleus, which receives extensive pain signals from the rest of the body. Dr. Keller is collaborating also with J. Marc Simard, MD, PhD *(see opposite page)* to study how traumatic brain injury affects the PAG and other brain circuits to produce chronic pain and post-traumatic stress disorder.

Joseph F. Cheer, PhD

Associate Professor, Department of Anatomy & Neurobiology

Dr. Cheer, a neurobiologist, is searching for ways to help addicts manage the often uncontrollable cravings that compel them to continue to use despite knowing that their behavior is self-destructive. He has focused on two neurotransmitters that play a major role in driving addictive behavior: dopamine and endocannabinoids. He has found that the two compounds are closely intertwined, and that curtailing the action of endocannabinoids also inhibits dopamine. Furthermore, his research indicates that this dual action may significantly ease cravings. In pre-clinical experiments, he has identified compounds that block endocannabinoid synthesis and significantly reduce the pharmacological effects of cocaine.

Mary Kay Lobo, PhD

Assistant Professor, Department of Anatomy & Neurobiology

Dr. Lobo and her team study the neurobiology of drug addiction. They focus on a region of the brain called the ventral striatum, which plays a central role in reward and motivation. They study two kinds of neurons that connect the ventral striatum to other areas of the brain. Both neurons respond to the neurotransmitter dopamine, but they have opposing tasks. One, known as the dopamine receptor 1 medium spiny neuron (D1-MSN), appears to have the potential to trigger addictive behavior. The other, the dopamine receptor 2 medium spiny neuron (D2-MSN), seems to be able to decrease drug-seeking behavior. Dr. Lobo is investigating how the two neurons interact in various kinds of addiction. Eventually, she hopes to find molecules that can modify D1-MSNs and D2-MSNs, with the goal of treating addiction.

Brain Disorders

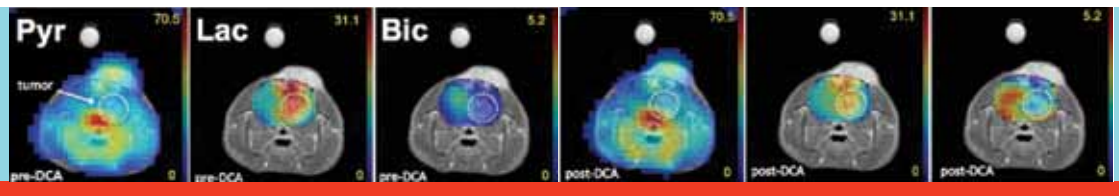
Scott Thompson, PhD

Professor and Chair, Department of Physiology

Dr. Thompson and his team have identified promising compounds that could successfully treat depression very quickly with minimal side effects. Although these compounds have not yet been tested in people, they could offer significant advantages over current antidepressant medications. "Our results open up a whole new class of potential antidepressant medications," says Thompson.

Dr. Thompson and his team focused on an inhibitory neurotransmitter called GABA. He and his team argue that in depression, excitatory messages in some brain regions are not strong enough. Because there is no safe way to directly strengthen excitatory communication, they examined a class of compounds that reduce the inhibitory messages sent via GABA. These compounds minimize unwanted side effects because they work only in the parts of the brain that affect mood.

The researchers tested the compounds in rats that were subjected to chronic mild stress that caused the animals to act in ways that resemble human depression. Giving stressed rats the compounds successfully reversed some depressive behaviors, and the beneficial effects of the compounds appeared very quickly, within 24 hours, much faster than current medications.



► BY DAVID KOHN

SOM Researchers Make Major Advances

Laura M. Rowland, PhD
Associate Professor, Department of Psychiatry

Schizophrenia is generally seen as a psychotic disorder. But many people with the illness also suffer from learning and memory problems. Dr. Rowland is focusing on this aspect of the disease, and is currently involved in several studies using a range of imaging technologies, including functional MRI and magnetic resonance spectroscopy (MRS), to examine how cognition differs among people with schizophrenia. She also uses imaging techniques to track brain changes among those with schizophrenia as the disease progresses throughout the lifetime. In addition, she is focusing on another lesser-known aspect of the disease: the fact that patients often have sleep disturbances. She is using imaging as well as cognitive testing to explore how sleep affects clinical symptoms, memory, and brain measures in those with the illness.

Jessica A. Mong, PhD
Associate Professor, Department of Pharmacology

Overall, women tend to suffer more from sleep disorders than men. Some researchers argue that these gender differences in sleep quality may originate in hormonal differences. Dr. Mong has been exploring this possibility, particular with the ovarian hormone estrogen. "We want to understand the link between estrogen, the brain, and sleep disorders," says Dr. Mong, who is a neuroendocrinologist. She has focused on two brain regions, the hypothalamus and another, lesser known spot called the pre-optic area. She has found that a certain part of pre-optic area is dense with estrogen receptors. "This is really exciting," she says, "because it implies that this might be a locus at which estrogen has its effect on sleep."

Robert Schwarcz, PhD
Professor, Department of Psychiatry

In recent years, scientists have focused increasingly on the neurotransmitter glutamate as a key player in schizophrenia. Research has found that people with this illness tend to have less glutamate signaling than people without the disease. Scientists have theorized that this decreased glutamate activity might be connected with a range of schizophrenic symptoms, especially cognitive problems.

But boosting glutamate on a large scale causes serious side effects, including seizures and nerve cell death. For several years, Dr. Schwarcz, a neuroscientist, has studied alternative strategies that raise glutamate levels in the brain. He and his colleagues have focused on kynurenic acid. People with schizophrenia have higher than normal levels of kynurenic acid in their brains; perhaps not coincidentally, the compound decreases glutamate and impairs cognitive functions.

In recent years, Dr. Schwarcz and his team began to test the idea that lowering kynurenic acid levels might elevate brain glutamate levels. They showed this in animal studies, and also found that a reduction in kynurenic acid improves cognition in animals that have cognitive deficits similar to those seen in schizophrenia. Because this mechanism is indirect, it seems not to trigger the same side effects that directly boosting glutamate does. He is now investigating substances that might produce the same results in humans.

Neuroinflammation

Alan I. Faden, MD
The David S. Brown Professor in Trauma, Department of Anesthesiology, and Director of the Center for Shock, Trauma & Anesthesiology Research (STAR) and the National Study Center for Trauma & EMS

David Loane, PhD
Assistant Professor, Department of Anesthesiology

Dr. Faden has worked for decades on brain trauma and how it causes damage. He argues that there is a widespread misunderstanding about the true nature of traumatic brain injury and how it causes chronic degenerative problems.

He and Dr. Loane propose that chronic brain damage and neuropsychiatric problems after trauma are to a large degree caused by long-term brain inflammation. They argue that even repeated concussive impacts or mild traumatic brain injury may trigger chronic brain inflammation that can persist for years and cause lasting damage. "Brain inflammation is a key issue, and it has been underemphasized," says Dr. Faden.

The good news: they also say that chronic brain inflammation related to traumatic brain injury may be treatable. Their recent research shows that some experimental drugs, as well as carefully controlled exercise programs, can block brain inflammation caused by traumatic brain injury.

J. Marc Simard, MD, PhD
Professor, Department of Neurosurgery

Every year, about 80,000 people in the U.S. suffer from subarachnoid hemorrhage (SAH), bleeding in the space between the brain and the tissues covering the brain. Neuroinflammation following SAH is closely linked to cerebral vasospasm, stroke and cognitive dysfunction. Dr. Simard's preclinical and clinical work over the last decade has identified novel molecular pathways and innovative therapeutic strategies to mitigate neuroinflammation, vasospasm and cognitive decline in SAH. In both patients with SAH and in animal models of SAH, the recently discovered Sur1-Trpm4 (sulfonylurea receptor 1 – transient receptor potential melastatin 4) channel is upregulated, and plays a previously unrecognized, and critical, role.

In animal models of SAH, the anti-diabetes medicine glibenclamide reduces markers of inflammation, as well as neuronal death, and significantly ameliorates cognitive dysfunction. The drug appears to work via the Sur1-Trpm4 receptor. Gene suppression also seems to affect this pathway. Other research has found that in animal models of SAH, a low-dose infusion of heparin can reduce neuroinflammation and neuronal apoptosis. In humans with severe SAH, heparin reduces the incidence of vasospasm, stroke and cognitive dysfunction. "Targeting neuroinflammation is crucial for reducing cognitive symptoms after SAH," says Dr. Simard.

Cutting Edge Therapies

Dennis Sparta, PhD
Assistant Professor, Department of Anatomy and Neurobiology

A neuroscientist, Dr. Sparta studies how addiction and stress affect the brain. He uses a new approach to better understand how different kinds of neurons behave in the brain. Known as in vivo calcium

[continued on back page]

BRAIN SCIENCE BREAKTHROUGHS

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imaging, this technology allows him to track individual neurons as they are activated; he attaches a tiny microscope to the heads of mice, and watches the neuronal activity in real time. Then he can see how the neuron reacts to particular situations, for example when the mouse experiences stress. So far, he has found links between certain kinds of neurons in specific brain regions, and has linked particular neuronal reactions to stressful situations.

Michael T. Shipley, PhD
The Donald E. Wilson, MD, MACP Distinguished Professor and Chair, Department of Anatomy & Neurobiology

On a cellular level, how does the brain organize itself? This is a fundamental question, one that is enormously complex. For the past several decades, Dr. Shipley, a neuroscientist, has focused on this daunting topic. Unlike many neuroscientists, he studies normal neurocircuitry rather than abnormal, in order to come to a baseline understanding of how the system operates before it goes awry. Using a mouse model, he analyzes the olfactory bulb, an area of the brain devoted to decoding and cataloguing smell—an especially crucial sense for the animals. He uses a cutting-edge technique that allows him to follow individual neuronal cells as they react to stimuli. He has mapped these cells onto larger patterns, and has so far delineated 3,000 neural circuits in the olfactory bulb.

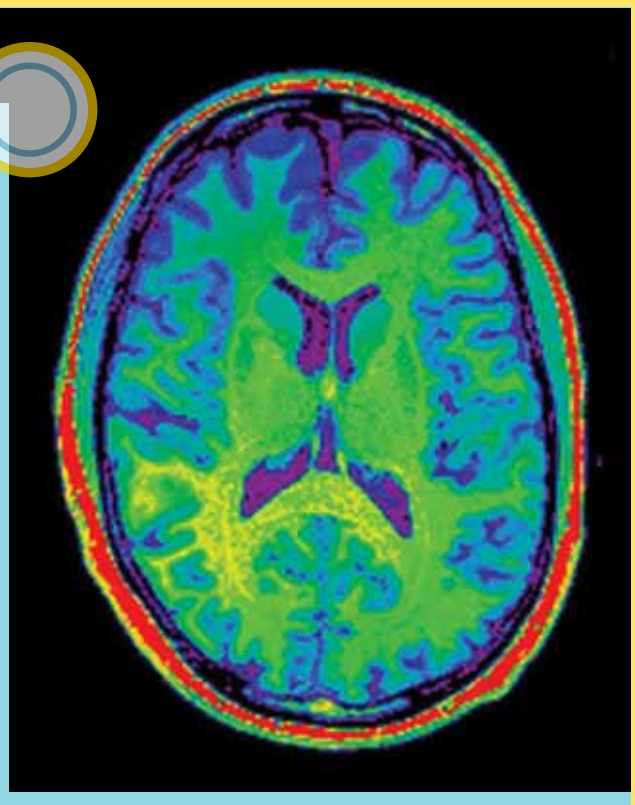
Graeme Woodworth, MD
Associate Professor, Department of Neurosurgery

It's often hard to identify brain tumors with current imaging technology. On top of that, for obvious reasons, exploratory brain surgery is fraught with problems. Dr. Woodworth and his colleagues at the Center for Integration of Metabolic Imaging and Therapeutics are working with a new approach to diagnosing this problem: they are using metabolic imaging, which detects specific physiological signatures of different kinds of tissue. For example, cancerous tissue metabolizes glucose differently than normal tissue. Using this approach, Woodworth can more accurately pinpoint which tissue must be removed.

Dr. Woodworth and his colleagues, who include Howard M. Eisenberg, MD, Professor and Chair in the Department of Neurosurgery, are also working on new approaches to removing brain tumors. Woodworth is working with focused ultrasound, a technology that uses sound waves to interact mechanically with tissue. Historically, ultrasound has been used for many purposes, including physical therapy and diagnostics. Dr. Woodworth and others are testing it as a way to disrupt and destroy cancerous tissue with unprecedented precision. The approach allows surgeons to test whether they have targeted the correct tissue for destruction. With other forms of surgery, such pre-testing is impossible.

Thomas Blanpied, PhD
Associate Professor, Department of Physiology

For more than a century, neuroscientists have known that nerve cells talk to one another across the small gaps between them, a process known as synaptic transmission. Information is carried from one cell to the other by neurotransmitters such as glutamate, dopamine, and serotonin, which activate receptors on the receiving neuron to convey the excitatory and inhibitory messages. Beyond this, how does synaptic transmission really work? That's what Dr. Blanpied is trying to unravel. Each synapse, the part of a neuron that transmits messages, contains between 300 and 1,000 different proteins. "Synapses are very complicated molecular machines," Dr. Blanpied says.



His lab has been trying to understand how these proteins fit together. His lab is using an innovative technology known as single molecule microscopy, which locates and tracks the movement of individual proteins in a living cell, and even within the confines of a single synapse. They have discovered an unexpected aspect to this architecture that may explain why synapses are so efficient but also susceptible to disruption during disease: at each synapse, key proteins are organized very precisely across the gap.

somnews
University of Maryland School of Medicine October 2015 Vol.17 No.2

SOMnews is produced by the University of Maryland School of Medicine, Office of Public Affairs
E. Albert Reece, MD, PhD, MBA , Vice President for Medical Affairs, University of Maryland, and Dean, University of Maryland School of Medicine ▲ Chris Hardwick, Executive Editor ▲ Caelie Haines, Managing Editor
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Submitting information to SOMnews: Please email your submission six weeks prior to the month you wish to see your submission included to Caelie Haines, Public Affairs Manager, at chaines@som.umaryland.edu.
Printed using environmentally-responsible low VOC inks.

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