GEISINGER Research Connections

Spring 2012

Linking the Research Community

Geisinger a Leader in the Emerging Field of Nanoproteomics

For Steven A. Toms, MD, MPH, FACS, every patient is a learning opportunity.

"At Geisinger, we are uniquely positioned to effectively view every patient who walks through the door as a study patient, as a research patient," noted the neurosurgeon and researcher. "For every patient who comes to us for their care, we have the opportunity to collect data in the electronic health record, sort it, analyze it for quality initiatives, and then run it through best-practices applications—such as the Geisinger ProvenCare® system—to ensure that the patient is getting the best possible care. With the MyCode® biobank, we collect biological samples, and soon we will be able to link genomic and proteomic data to our health records and move ever closer to the ultimate goal of personalized medicine.

"That's the reason I was excited to come to Geisinger, and why I am so excited about the future here," he added. Dr. Toms joined Geisinger Health System as associate chief medical officer and director of the department of Neurosurgery in 2007.

From Genomics to Proteomics

Much of his optimism stems from the work Dr. Toms has brought with him to Geisinger and the team he has recruited to build on it. His research focus started in the field of genomics but has transitioned over the years to proteomics, which he describes as "the study of

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Research Collaboration Seeks To Identify New Therapeutic Targets for Epilepsy

The National Institutes of Health estimates that roughly three million Americans (1% of the population) have been diagnosed with some form of epilepsy, making it the third most common neurologic disorder, behind Alzheimer's disease and stroke, in the country. The incidence of epilepsy in the central and northeast Pennsylvania area mirrors that of the nation. However, what is most troubling, according to Frank Gilliam, MD, Director, Department of Neurology and Director, Epilepsy Program, Geisinger Health System, is that some 40% of those with epilepsy have a form of the disorder that cannot be controlled by currently available pharmacotherapy. As a result, they continue to suffer from debilitating and life-threatening seizures that affect their quality of life and potentially may lead to problematic comorbidities, including depression and loss of cognitive function.

It is this group of epilepsy patients—those who suffer from pharmacoresistant or intractable epilepsy—that is the focus of the research being performed by Dr. Gilliam and his colleague on the basic research side, Janet Robishaw, PhD, Associate Director and Senior Scientist, Weis Center for Research.

"I think there's a mistaken impression that

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An Introduction from David H. Ledbetter, PhD Chief Scientific Officer

Given that the brain and the nervous system are the most complex systems of the body, it is no surprise that diseases of the brain and nervous system are complex and varied, including brain tumors, addiction, anxiety disorders, dementia, epilepsy, intellectual disabilities, autism, depression, schizophrenia, Parkinson's disease, stroke, traumatic brain injury, and others too numerous to list. The number of diseases, the debilitating and often chronic nature of these diseases, and the lack of effective treatments result not only in considerable patient suffering, but also tremendous cost. In the only study of its kind, researchers in the United Kingdom estimated that "brain disorders cost $1 trillion a year, more than cancer, cardiovascular disease and diabetes put together."

Neuroscience research is critical to understanding the basic biology of the brain and to discovering new and better treatments. Broadly defined as the study of the brain and the nervous system, neuroscience is – as is demonstrated in this issue of *Research Connections* – a highly interdisciplinary area that requires the contributions of different approaches and techniques from the molecular and cellular levels to the systems and cognitive levels. Together, they allow neuroscientists to answer questions about how the brain and nervous system work, how they develop, and what can go wrong.

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Research Unravels the Workings of the ErbB3 Receptor and Its Effects on the Peripheral and Central Nervous Systems

Research at Geisinger Health System is attempting to solve some of the mysteries of the peripheral nervous system (PNS), the part of your nervous system that's not your brain or spinal cord. The PNS's main function is to carry sensory signals from your body to your brain, and to carry motor signals from your brain to your muscles. The PNS contains two main types of cells: neurons (or nerve cells) that actively conduct the electrical sensory or motor signals; and Schwann cells (also called glial cells) that associated closely with neurons and significantly increase the rate of signal conduction. One way they do this is by forming a fatty sheath, called myelin, around nerve fibers. Myelin sheaths provide insulation and increase both the speed and efficiency of nerve impulse conduction. Defects in either neurons or Schwann cells can cause severely debilitating diseases, the peripheral neuropathies.

One team of researchers, led by Nikolaos Tapinos, MD, PhD, Director of Molecular Neurosurgery Research and a Staff Scientist at the Sigfried and Janet Weis Center for Research, is focused on the potential role of a newly identified variant of a key PNS signaling protein, the ErbB3 receptor tyrosine kinase. ErbB3 is essential for the development of Schwann cells, including their ability to interact with nerve cells.

Dr.Tapinos and his research team were the first to identify the nuclear variant of ErbB3, which they believe regulates expression of target genes that are needed for normal PNS function. He and collaborators from the Albert Einstein School of Medicine in New York believe their research will ultimately lead to a better understanding of how traumatic injuries affect the nerves in both the PNS and the central nervous system. Their initial findings were published in the March 30, 2011 issue of *The Journal of Neuroscience* (2011;31:5106-5119).

"I have always been interested in how the nervous system works, and by that I mean how the cells—the neurons and glia—communicate with each other," said Dr. Tapinos, who joined Geisinger in 2007. "This communication is obviously disrupted in certain disease states and pathologies, and if we can determine the cause of this disruption, we can better understand these pathologies and, potentially, identify therapeutic targets."

Dr. Tapinos' interest in the ErbB3 protein dates back to his time as a postdoctoral fellow at Rockefeller University in New York, where he worked in a laboratory studying leprosy bacteria, which infects the PNS and produces peripheral neuropathies in humans. One of the proteins he studied was the ErbB3 receptor.

Although he no longer works on leprosy bacteria, Dr. Tapinos has continued to delve into the exact function of the ErbB3 protein in the PNS. It is already known that this protein is vital to the development of the PNS. Its communication with another critical signaling protein, the neuronal neuregulin-1 type III protein, determines how Schwann cells interact with the axons in the PNS and form myelin.

"This signaling axis between neuregulin and ErbB3 is the most important one in the general biology of Schwann cells and the PNS," said Dr. Tapinos. "Because

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Research in Human Brain Tumors and in Injectable Hydrogels

In addition to his continued work with ErbB3, Dr. Tapinos is also working with fellow Geisinger researchers and physicians Atom Sarkar MD, PhD and Jonathan Slotkin, MD from the department of neurosurgery. His work with Dr. Sarkar is focused on studying the molecular, mechanical and epigenetic mechanisms that control migration of human glioblastomas. Their work has revealed a novel signaling pathway, which regulates migration, and they currently develop a mouse model where inhibition of this pathway will be evaluated as a potential future treatment for patients with glioblastoma. The study with Dr. Slotkin is designed to assess the use of biocompatible injectable hydrogels for the controlled release of drugs for the treatment of chronic pain caused by compression-induced peripheral nerve damage. The study will compare the resulting molecular and behavioral impact in rodents receiving the injectable scaffold with drug therapy. InVivo Therapeutics, manufacturers of this novel hydrogel technology, is funding the study.

"In all these areas, we have to establish the animal models first but, obviously, translating our findings to human beings is the ultimate goal," Dr. Tapinos said. "I love basic research but, because of my background as a medical doctor, I want to see how our findings will impact medical care. For me, that's a very big advantage of working at Geisinger. There is a connection of basic research to the clinic. We are all on the same campus, and the doctors here are very open to collaboration with basic scientists. When we are ready to transfer our research to humans, we have a large database of human tissue available. The potential is very exciting."

Research Unravels the Workings of the ErbB3 Receptor

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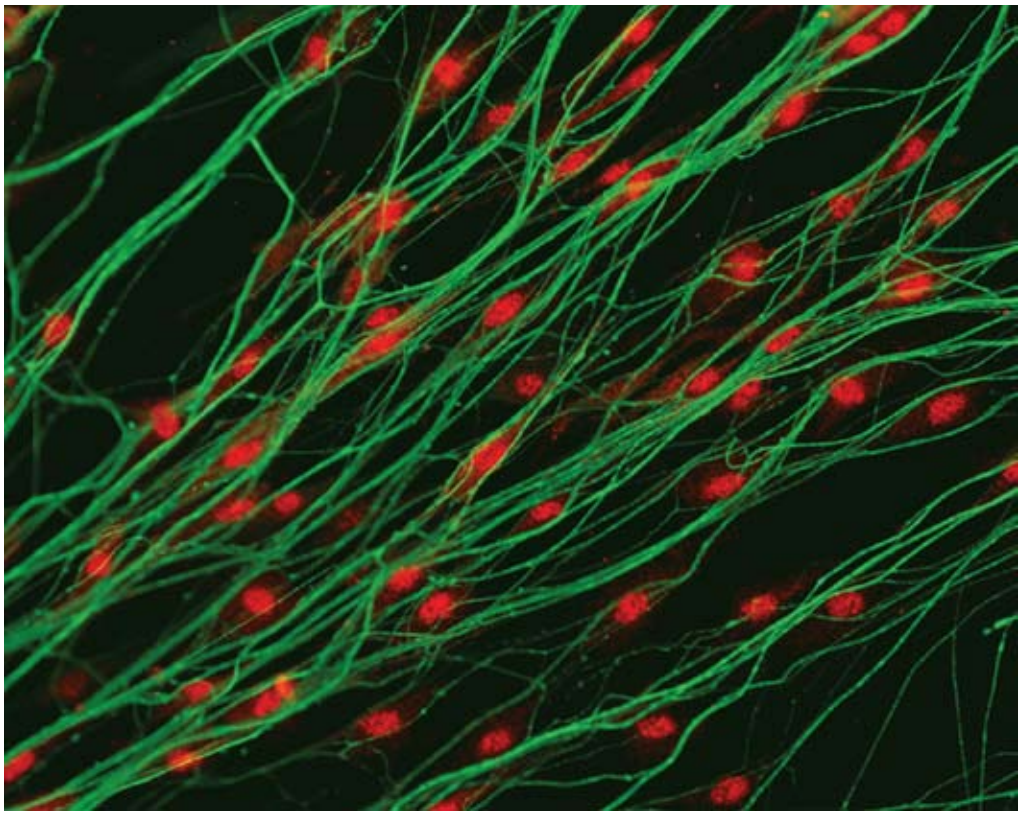
of the existence of animal models with conditional deletion of ErbB3 or neuregulin in the PNS, we now know that ErbB3 is very important in the maintenance and correct function of the nervous system."

ErbB3 in Neuronal and Cancer Pathologies

The exact role of the nuclear variant of ErbB3 remains to be determined, although Dr. Tapinos hopes to change that. In 2010, he received a 5-year, $1.8 million grant from the National Institutes of Health to finance his research efforts. In the paper published in *The Journal of Neuroscience*, he and his colleagues revealed their initial findings, which indicate that the nuclear variant of ErbB3 plays a "distinct role in the regulation of Schwann cell myelination." Dr. Tapinos and his colleagues believe that this nuclear variant of ErbB3 may play an important role in the development of neuronal pathologies, and perhaps in the development and progression of some cancers.

"We are the first ones to describe the nuclear variant of the ErbB3, and the first to describe the potential mechanisms behind its formation as well as its role in Schwann cell myelination," said Dr. Tapinos. "Now we are collaborating with a group in France that has found that in Schwannomas [Schwann cell tumors] there is a very high expression of nuclear ErbB3. So it seems that nuclear variant ErbB3 has not only a role in Schwann cell physiology and in communication between Schwann cells and axons in the nervous system, but also a separate role in cancer as well. Gaining additional understanding of this potential role for nuclear variant ErbB3 is now the focus of our [ongoing] research."



Schwann cells (red) expressing nuclear ErbB3 as they associate with Dorsal Root Ganglion axons (green, labeled for neurofilament).

According to Dr. Tapinos, the team, which includes his lab as well as his collaborators at Albert Einstein School of Medicine, has already performed genome-wide screening to determine the specific DNA motif that nuclear ErbB3 binds in the nucleus of Schwann cells.

The group's findings to date have already achieved a level of acclaim within the biomedical research community. The article in *The Journal of Neuroscience* was given the distinction of being selected by the Faculty of 1000 (F1000) for inclusion in its list of the most important articles in biomedical research in 2011. The F1000 is a collaboration that provides post-publication peer review, in which research is selected from a global "faculty" of leading scientists and clinicians. The F1000 honor is bestowed on approximately 2% of all articles published in peer-reviewed journals. The research by Dr. Tapinos and his team was nominated by British neuroscientist Kristjan R. Jessen, PhD, whose work has focused primarily on peripheral neuropathy; he believes Dr. Tapinos' findings have implications for his work as well as those of others dealing with PNS-related pathologies.

Gerda E.Breitweiser, PhD, Senior Scientist in the Weis Center for Research, also recently had an article selected by the Faculty of 1000 (F1000). The article, *Agonist-driven maturation and plasma membrane insertion of calcium-sensing receptors dynamically control signal amplitude*, appeared in *Science Signaling*. It was selected and evaluated by Daniela Riccardi, PhD, Member of the F1000.

Collaboration Seeks To Identify New Therapeutic Targets for Epilepsy

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epilepsy is one of those curable diseases," noted Dr. Robishaw. "What many people don't realize is that the drugs we have available today don't address the underlying neurologic problems that cause epilepsy. They only mitigate patients' seizures, and even for that they are not always effective. So really, in the management of epilepsy, we are in no better position today than we were 30 years ago. We still have a long way to go toward understanding the complex etiologies of epilepsy disorders and developing more effective strategies to treat them."

Drs. Gilliam and Robishaw hope to change that. Although as many as 40 hospital centers across the country are performing surgical procedures on epilepsy patients, only a handful—a group that now includes Geisinger—are using an innovative approach that effectively maps out patients' brains prior to surgery, thereby identifying an area called the "epileptogenic zone," which Dr. Gilliam describes as the "area with the highest density of interictal spikes." Interictal refers to the period between epileptic seizures.

Prior to surgery, patients undergo EEG testing and monitoring for several days so that Dr. Gilliam and the neurosurgeons under the leadership of Dr. Toms can identify three distinct regions of the brain in epileptic patients, all of which will ultimately be removed during surgery. The area the team calls "Region One" is the area where the most frequent spiking occurs. "Region Two," an area typically less than half an inch from "Region One," also has a high degree of spiking, but it is not directly involved in the onset of the patient's seizures; it is removed during surgery to improve the patient's odds of remaining seizure-free. Finally, "Region Three" encompasses areas surrounding regions one and two that will also be resected, similar to the "margins" surgeons take when removing tumors.

"Geisinger is one of a select group of hospitals providing this level of intervention at this volume," said Dr. Gilliam, who came to Geisinger from NewYork-Presbyterian Hospital in 2009 to head up the system's fledgling epilepsy program. In 2011, Drs. Gilliam and Toms coordinated 55 of these procedures on 37 different patients. Roughly 80% of these patients have been seizure-free ever since.

With patient consent, tissue collected from all three regions during surgery will be stored in a biobank for use by Dr. Robishaw's lab. Using a new technique called RNA Seq, Dr. Robishaw and her team will extract RNA from the tissue samples and analyze it. Since inception of this project late last year, the team has already banked tissue from eight patients.

"The biobanked tissue will enable us to quantify gene expression changes and to identify novel spliced products in the active seizure zone versus the adjacent silent zone," explained Dr. Robishaw. "Ultimately, these results will identify seizure-related genes and networks that can be developed as therapeutic targets to block the epileptogenic process."

"We are attempting to do more complete mRNA expression analysis of the tissue so that we can be more precise in the way we define the localization of the seizure onset zone," added Dr. Gilliam. "Our hope is that a better understanding of the neurobiology of the human epilepsy will help us develop improvements in treatment. And it's possible we could identify proteins at work in, or characteristics of, the epileptic zone that we could use as a target for various interventions—either surgical or pharmacologic—to reduce patients' seizures."

Research has already shown that only a small percentage of those patients who suffer from epilepsy have a form of the disorder where the cause can be pinned on a single gene—or a "Mendelian cause," as Dr. Robishaw puts it. It is here that Drs. Gilliam and Robishaw hope that the latter's ongoing work on epilepsy in mouse models can help inform the clinical research. According to Dr. Robishaw, she and her team have already identified a synergistic interaction between two defective signaling pathways that may be common to human epilepsies. As a result, when the initial RNA Seq data are obtained, they will be focusing on these two signaling pathways that work together in a neural network—what Dr. Robishaw calls a signaling hub—and hopefully identifying variants in this network that work together to explain the polygenic basis for most human epileptic disorders.

Neuroradiologist Works to Improve Patient Care and Outcomes with Advanced Imaging and Informatics

Gregory James Moore, MD, PhD, worked for more than 12 years as an MIT-trained engineer, magnetic resonance physicist, and neuroscientist before studying to become a physician. As a result, he has a unique perspective on what he sees as an ongoing disconnect between research and clinical practice across the healthcare community. He believes the culture at Geisinger Health System endeavors to bridge that divide.

"Geisinger uniquely positions researchers to make a difference in patient care," said Dr. Moore, a pediatric and adult neuroradiologist who joined the health system as vice chair of systemwide radiology for research and informatics in autumn 2010. "At Geisinger I won't just be designing advanced tools for use in the research lab but also implementing those tools in a way that can impact patient care."

Abigail Geisinger Clinician Investigator

Dr. Moore is one of several Geisinger physicians and clinical investigators to be granted the Abigail Geisinger Clinician Investigator designation. Named for Geisinger's founder, the designation recognizes clinical investigators who bring a unique research perspective and focus to the hospital. With his expertise in neuroimaging—from, as he puts it, a "functional, anatomical, and neurochemical" perspective—Dr. Moore aims to do just that. Throughout his career he has strived to "go beyond routine neuroradiology" to develop and implement advanced neuroimaging tools to improve the diagnosis and treatment of children and adults with brain disorders and trauma.

"Consistent with Geisinger's recently developed 10-year research strategic plan, with its focus on personalized health research, the Abigail Geisinger Clinician Investigator program is key to our ability to recruit and retain the best and brightest clinicians committed to high-quality patient care who are also highly talented clinical investigators," said David H. Ledbetter, PhD, FACMG, executive vice president and chief scientific officer. "Dr. Moore is an unusually talented physician-scientist with expertise in both neuroimaging and informatics who has led significant National Institutes of Health–funded research programs at other great academic institutions. We are very fortunate to have him at Geisinger and to have him set such a high bar for the quality of investigators in the Abigail Geisinger Clinician Investigator program."

Before joining Geisinger, Dr. Moore was the lead author of a landmark longitudinal magnetic resonance imaging (MRI) study published in *The Lancet* (2000;356:1241-1242) that was the first to describe a pharmacologic-induced increase of neurotrophic effects in the human brain. Since that time, much of his research has focused on developing and validating advanced neuroimaging biomarkers for improved diagnosis and to predict and monitor treatment response in children and adults with devastating brain illness (including neurodegenerative disorders such as Alzheimer's disease), developmental disorders in children with autism, and neuropsychiatric disorders (including bipolar disorder, depression, and obsessive-compulsive disorder).

Additionally, Dr. Moore also has been leading efforts at Geisinger to implement "quantitative neuroimaging" approaches that will assist in the diagnosis and management of disorders ranging from temporal lobe epilepsy to autism and attention deficit-hyperactivity disorder. These approaches enable physicians to analyze what he describes as "subtle abnormalities" in patients' brains—such as hippocampal volume in those with temporal lobe epilepsy—and, potentially, identify therapeutic targets. In a recent study published in the journal *Radiology* (2012;262:216-223), for example, he and his collaborators found that spinal canal subdural hemorrhage was a common and sensitive neuroimaging marker for abusive head trauma (i.e., shaken baby syndrome).

"My overall research focus is really to lead the discovery, development, and validation of advanced neuroimaging biomarkers using advanced neuroimaging tools, including three-dimensional quantitative volumetric MRI, functional MRI, and quantitative magnetic resonance spectroscopy—essentially a noninvasive biopsy of the brain," Dr. Moore said. "On the patient care side, we can couple the information we get from imaging with neuroinformatics technology to improve diagnosis, guide intervention, and predict treatment response in children and adults with brain disorders or injury."

Center for Autism Research and Treatment

Dr. Moore also will be involved in several major new initiatives at Geisinger, including a project involving the study and treatment of children with autism and other developmental disorders, including those with mental retardation and cerebral palsy, called the Center for Autism Research and Treatment. This major new research and clinical center currently is being developed under the leadership of Dr. Ledbetter. Within the program, neuroscientists (including experts in neurobehavioral pediatrics, clinical and educational psychology, neuroimaging, genetics, and computational sciences)—as well as other specialists—will work collaboratively on efforts to improve the diagnosis and management of children with autism and other developmental disorders. Dr. Moore's role will be to lead the advanced neuroimaging clinical and research components of this project and

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Research Aims to Assess Addiction Liability in Pain Patients

The abuse and misuse of opioid analgesic pain medications has become a seemingly intractable problem in the management of patients with chronic noncancer pain (CNCP). Clinicians treating this patient population face many challenges. Among them: how to effectively and efficiently identify those patients at the highest risk for developing an addiction during the course of their treatment prior to the initiation of therapy.

Ongoing research, under the leadership of Joseph A. Boscarino, PhD, MPH, senior investigator at the Center for Health Research, and director, Clinical Research Training at Geisinger Health System (GHS), aims to address this complex issue. He and his team are currently engaged in studies designed to assess the genetic and environmental risks for addiction to prescription opioids.

"Our goal is to identify personality traits and/or a genetic biomarker that would be an effective predictor of addiction liability and to make the process efficient for application in the clinical setting," said Dr. Boscarino, an epidemiologist and social psychologist who joined the Geisinger team in 2005. "Right now, we already know several predictive risk factors for addiction liability. However, the process for identifying these risk factors in patients currently requires a long diagnostic interview. Most clinicians simply do not have the time to perform that interview, so we need to find a more efficient method."

"Ultimately," Dr. Boscarino added, "the purpose of our work is to identify predictive factors for addictive liability, and to provide clinicians with a way to obtain this information quickly and cost-effectively. If a clinician has this information about their patient, they may decide to not prescribe an opioid, to prescribe a different drug, or to closely monitor the patient on opioid therapy. Knowing this information could have a huge impact on the problem of addiction in pain management."

A study involving 705 patients with CNCP from GHS is ongoing. Dr. Boscarino and his collaborators—including John J. Han, MD, director, Interventional Pain Management—have already published noteworthy preliminary findings from this patient population. For example, in an article published last year in the *Journal of Addictive Diseases* (2011;30:185-194), they revealed that the prevalence of opioid-use disorder (as defined by the Diagnostic and Statistical Manual of Mental Disorders) among these patients was 34.9% higher than rates identified in previous studies. Dr. Boscarino attributes this difference to the enhanced diagnostic procedure used to assess for addiction in this study and believes other studies would have had similar findings if they too had used the same criteria. To confirm this, he and his team are repeating the study on a similar patient population at New York University-Bellevue Hospital. Dr. Boscarino is an adjunct professor at Mount Sinai School of Medicine (pediatrics and internal medicine) in New York City and at Temple University School of Medicine (psychiatry) in Philadelphia.

Using the same GHS patient population, the team also published findings in the journal *Addiction* (2010;105:1776-1782), indicating that patients with a previous diagnosis of depression or a history of psychotropic drug use may be at higher risk for prescription opioid addiction while undergoing treatment for CNCP. For this aspect of the study, the researchers were given access to the participating patients' electronic health records (EHR) and asked the patients to provide DNA samples. As work in this area continues, the team hopes to identify specific genetic biomarkers for addiction liability, noted Dr. Boscarino.

"We already know from previously published studies that patients who have abused drugs such as marijuana or heroin in the past are likely to abuse opioids for pain management," he continued. "In our study, we found that patients with a history of mental health problems, or those who have been prescribed antidepressants in the past, are at higher risk. This is information that can be and should be available in the EHRs of all patients, and we're working toward that now. We see this as a pilot study, or a proof-of-concept study. We wanted to show the benefits of EHRs, and also that patients would provide their DNA. Now we hope to get funding to expand this research and develop a standardized approach for accessing this information.

New Investigator Profile: Atom Sarkar, MD, PhD

Given his name, one could argue that Atom Sarkar, MD, PhD, was born to be a scientist. If so, the New York native has indeed fulfilled that prophesy. Steven A. Toms, MD, MPH, FACS, associate chief medical officer and director of the department of Neurosurgery, calls Dr. Sarkar one of the "top young research neurosurgeons in the country." Dr. Sarkar brings that experience and an expertise in nanomedicine to GHS, where he works as a senior investigator in the department of Neurosurgery as the director of Stereotactic and Functional Neurosurgery while heading the Nanomedicine Laboratory at the Sigfried and Janet Weis Center for Research.

"With Dr. Toms, as well as Dr. Slotkin, who heads our spine division, and myself, we might have the largest collection of neurosurgeons interested in nanotechnology in the country," said Dr. Sarkar. "Nanomedicine is such a nebulous term. Really, we are attempting to find out what happens in disease, such as brain tumors, at the most basic level. We are trying to study the smallest molecules and see how they interact."

Dr. Sarkar comes to Geisinger after 5 years at The Ohio State University, where he ran his own lab and served as director of Tumor, Stereotactic and Functional Surgery, as well as director of Neurological Nanomedicine. While there, his research focused on, among other things, the use of "carbon dot" technology. Carbon dots—types of quantum dots—are fluorescent nanoparticles that are roughly 10 nm in size. Drs. Sarkar, Toms, and Slotkin will be attempting to use these particles to, as Dr. Toms noted, "label" tumors and other pathologies. At Geisinger, Dr. Sarkar will be leading the efforts to apply the technology for use in the diagnosis, analysis, and treatment of brain tumors and neurodegenerative disorders such as Parkinson's disease.

"We might use them to detect tumors or to deliver some payload—to use a military term—which may entail drug delivery," said Dr. Sarkar. "Everything is on the table."

"There are maybe five neurosurgeons in the country with this expertise," added Dr. Toms. "To bring in someone of Dr. Sarkar's ability and expertise was a unique opportunity for Geisinger."

New Investigator Profile: Jonathan Slotkin, MD

Jonathan Slotkin, MD, has joined the Geisinger Health System (GHS) as director of Spinal Surgery and director of Spinal Cord Injury Research in the department of Neurosurgery. He comes to GHS from the Washington Hospital Center in Washington, DC, and was recruited to the health system in November 2011 by Steven A. Toms, MD, MPH, FACS, associate chief medical officer and director of the department of Neurosurgery.

"With Dr. Slotkin, we now have three neurosurgeons who do nanotechnology work at Geisinger," noted Dr. Toms. "Dr. Slotkin trained at Harvard and, along with a group at MIT (Massachusetts Institute of Technology), developed a nanolevel scaffolding technology designed to repair damage from spinal injury. Dr. Slotkin has brought some of that work here and will be working to apply this technology in a peripheral nerve injury setting."

Indeed, Dr. Slotkin has devoted much of his career to research into the role of "quantum dot" nanoparticles in the nervous system, a research interest he shares with Dr. Toms. He has focused much of his work on the application of novel biomaterials—such as the new scaffolding technology, which is now in development at InVivo Technologies, a publicly traded medical device company—for drug delivery in the nervous system. In addition to his role at Geisinger, Dr. Slotkin also serves as the Medical Director on the Scientific Advisory Board at InVivo. In this role, he has fostered a corporate partnership between GHS and InVivo that will finance research designed to assess the use of the novel biocompatible injectable hydrogels in the controlled release of drugs

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Steven A. Toms, MD, MPH, FACS

Atom Sarkar, MD, PhD

Jonathan Slotkin, MD

Improve Patient Care and Outcomes with Advanced Imaging and Informatics

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to correlate imaging findings with the detailed genomic information from these patients in order to develop improved diagnostic and therapeutic strategies. According to Dr. Ledbetter, Dr. Moore will "add state-of-the-art structural and functional brain imaging expertise as well as high-performance computing and informatics for the big datasets derived from imaging and genomics data.

"My hope is that we can help inform the research direction and identify a neuroimaging phenotype for these disorders which will result in improved outcomes for these children," he added.

Finally, Dr. Moore also will lead an effort to develop rapid image-guided neurochemical and molecular interventions, which could lead to significantly improved outcomes in patients with stroke, patients undergoing treatment for brain cancers, patients with brain trauma, and in neonates with hypoxia at birth. As Dr. Moore noted, there is often a significant time lag bringing validated research findings into the clinic to help improve patient outcomes. The rapid image-guided neurochemical and molecular intervention program will provide neuroscience physicians with a key tool required to intervene in these complex patients with novel therapeutic interventions. Dr. Moore has already worked with Geisinger System Radiology Chair John F. Cardella, MD, and others at Geisinger to help bring a state-of-the-art 3T high-field MRI scanner to the campus, which is a key technology required for this program.

On a practical level, the Abigail Geisinger Clinical Investigator designation will allow Dr. Moore to focus on these and other clinical efforts. One of the hallmarks of the program is the support it provides clinical investigators both financially and collaboratively.

"It is quite an honor for me to have Abigail Geisinger's name attached to my work," said Dr. Moore. "Her charge was: 'Make my hospital right; make it the best.' For me, that means bringing and applying the most promising research findings and emerging technologies in the areas of advanced imaging and informatics to improve patient care and outcomes. I share her vision and passion and believe this unique clinician-investigator program provides an opportunity for us to truly transform current diagnostic and treatment approaches in the neurosciences and to continue our national leadership role in clinical innovation."

New Investigator Profile: Jonathan Slotkin, MD

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for the treatment of chronic pain resulting from compression-induced peripheral nerve damage. For this project, Dr. Slotkin will be working with Nikolaos Tapinos, MD, PhD, director of Molecular Neurosurgery Research at GHS.

Drs. Slotkin and Tapinos also have submitted an application for a Small Business Technology Transfer grant from the National Institutes of Health to fund additional research into the safety and efficacy of the injectable scaffold technology. According to Dr. Slotkin, the injectable hydrogels could potentially enhance or replace the current technology used in epidural injections and nerve blocks, procedures performed on millions of patients in the United States.

"This technology could provide a sustained, controlled release of drugs for pain caused by compression-induced peripheral nerve damage," said Dr. Slotkin. "This is a prime example of translational research, and the ability to do this type of work is one of the main reasons I came to Geisinger. I am part of a team of people who work at the highest levels of neurosurgery, with experience in teaching, research, patient care, and administration. That, coupled with Geisinger's national reputation as a process improvement leader and best practices leader, made this an opportunity I could not pass up."

Geisinger a Leader in the Emerging Field of Nanoproteomics

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proteins and how they interact in disease states." Specifically, Dr. Toms has helped to pioneer the field of nanoproteomics, which involves the application of high-throughput nanotechnology, such as mass spectroscopy, in proteomic research and analysis. The technology allows researchers to study how proteins and the various peptides within them interact in a number of disease states, including cancer.

Dr. Toms was involved in some of the initial studies using nanotechnology in proteomics, specifically in glioblastoma, an area of interest during his days at Vanderbilt University Medical Center (*Cancer Res.* 2005;65:7674-7681 and *Clin Cancer Res.* 2004;10:981-987). From 2006 to 2010, he served as the Section Editor for Surgical Techniques and Implantable Devices in the Wiley Interdisciplinary Review publication *Nanomedicine and Nanobiotechnology*.

"My specific interest in nanoproteomics is really an outbranching of some of the genomic work I've done in the past," he noted. "I realized genomics wasn't close enough to the clinical problems that we see. We really need to see how the proteins created from these genes interact within the cells to develop pathological hallmarks of diseases such as cancer. I feel that the closer we get to seeing how a cancer cell responds to changes in different protein patterns, the closer we'll be to understanding diseases."

Because of his status in the field, he and his longtime collaborator, Robert Weil, MD, of Cleveland Clinic, were recently appointed by Springer to serve as Professional Editors of *Nanoproteomics: Methods and Protocols*. The 23-chapter volume is the latest installment in the company's series entitled *Methods in Molecular Biology*, a compendium of work by some of the leading minds in the emerging field. According to Dr. Toms, it is designed to help researchers as they attempt to incorporate and standardize nanoproteomic approaches in their laboratories. The text is divided into five sections covering preliminary sample preparation, nanoscale fluidic devices and methods, nanostructured surfaces and nanomaterials, and nanoproteomic techniques to detect and understand proteins and proteomic alterations specific to human pathology.

"I call it a toolkit or cookbook for nanoproteomics for the basic science lab," Dr. Toms said. "Proteomics has really evolved over the past 15 years, along with the introduction of nanotechnology. Many labs are still trying to standardize the procedures for using this technology."

'Quantum Dots'

Dr. Toms' research in the field of nanoproteomics is ongoing. At present, he and his collaborators are using optical nanoparticulates called "quantum dots" to attempt to "label" tumors and other disease states for optically guided surgical resection of cancers and inflammatory lesions. The work is designed to expand on the findings of another of Dr. Toms' longtime collaborators, Marcel P. Bruchez, PhD, who was involved in the development of these small—roughly 10 nm in size—fluorescent particles. In addition to enhancing pathologic analysis, the quantum dots may ultimately be used in drug delivery and other treatment approaches.

"It is a technique to light-up pathology," said Dr. Toms. "These particles are water soluble and can be used in biological interactions to effectively light up tumors and other pathologies. Now, we are working to see how the human body manages these particles, how they pass through the bloodstream, and how the body secretes them. Ultimately, we want to see if we can target them to specific tumors and apply them for surgical use."

To assist him in this work and other applications of nanotechnology, Dr. Toms has recruited to Geisinger two of the top young minds in neurosurgical research—Atom Sarkar, MD, PhD, and Jonathon Slotkin, MD, both featured in new investigator profiles in this issue of *Research Connections*. Both bring with them a history of well-recognized research in the field of nanomedicine. Dr. Sarkar, for example, worked with carbon dots in his own laboratory at The Ohio State University. Dr. Slotkin's work in recent years has focused on the use of nanotechnology in drug delivery for the management of chronic noncancer pain.

"With these two additions to the team, we now have three of the maybe five neurosurgeons in the country doing this type of work," said Dr. Toms. "Geisinger is a small research enterprise compared with Harvard or Penn; we're never going to have 500 research labs here in Danville. But we want to recruit people who can compete with those labs, with the best neurosurgeons and researchers in the country, and provide patients with access to clinical trials they might have only found at big city hospitals in the past. The ability to bring in people of the quality of Drs. Sarkar and Slotkin is a testament to Geisinger. We really have created an environment where creative and entrepreneurial people who are also outstanding in medical care and surgical technique can thrive and do the highest levels of research."

Staff Publications

These publications feature Geisinger employees as authors, with publication dates from December 2011 through March 2012. The Geisinger author's name is bolded. The listings below follow National Library of Medicine format.

1. **Antohe JL, Bili A, Sartorius JA, Kirchner HL, Morris SJ, Dancea S**, Wasko MCM. Diabetes mellitus risk in rheumatoid arthritis: reduced incidence with anti-tumor necrosis factor & therapy. Arthritis Care & Research. 2012 Feb. 64(2):215-221.

2. Berger JS, Herout PM, Harshaw Q, **Steinhubl SR**, Frye CB, Becker RC. "Bleeding-associated outcomes with preoperative clopidogrel use in on- and off-pump coronary artery bypass." J Thromb Thrombolysis. 2012 Feb 16. [Epub ahead of print]

3. Bhatt, DL, Pare G, Eikelboom JW, Simonsen KL, Emison, ES, Fox KAA, Steg G, Montalescot G, Bhakta N, Hacke W, Flather MD, Mak KH, Cacoub P, Creager MA, **Berger PB, Steinhubl SR**, Murugesan G, Mehta SR, Kottke-Marchant K, Lincoff AM, Topol EJ, on Behalf of the CHARISMA Investigators. The relationship between CYP2C19 polymorphisms and ischaemic and bleeding outcomes in stable outpatients: The CHARISMA genetics study. European Heart Journal. Eur Heart J. 2012 Mar 26. [Epub ahead of print]

4. **Bili A**, Morris SJ, Sartorius JA, **Kirchner HL**, Antohe JL, Dancea S, Wasko MC. Tumor Necrosis Factor-α Inhibitor Use Is Not Associated with Lipid Changes in Rheumatoid Arthritis. J Rheumatol. 2012 Apr 1. [Epub ahead of print]

5. **Blankenship JC**, Moussa ID, Chambers CC, Brilakis ES, Haldis TA, Morrison DA, Dehmer GJ. Staging of multivessel percutaneous coronary interventions: an expert concensus statement from the Society for Cardiac Angiography and Interventions. Catheterization and Cardiovascular Interventions. 2011 Epub Nov 9.

6. **Boscarin JA, Erlich PM, Hoffman SN, Zhang X**. Higher FKBP5, COMT, CHRNA5 and CRHR1 Allele Burdens are associated with PTSD and Interact with Trauma Exposure: Implications for Neuropsychiatric Research. Neuropsychiatric Research and Treatment 2012; 8: 131-139.

7. **Boscarino JA, Kirchner HL, Hoffman SN, Sartorius J**. Use of the New York PTSD Risk Score to predict PTSD: Current and future research efforts. General Hospital Psychiatry 2012 Feb 9. [Epub ahead of print].

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12. Chute CG, Huff SM, Ferguson JA, **Walker JM**, Halamka JD. There are important reasons for delaying implementation of the new ICD-10 coding system. Health Affairs. 2012 Apr. 31(4):1-7.

13. **Dalton SR, Hicks M, Shabanowitz R, Elston DM**. Ethical dilemmas in the management of tumor-stage mycosis fungoides in a pregnant patient. Journal of the American Academy of Dermatology. 2012 Apr. 66(4):661-663.

14. **Dehdashti AR**, Binaghi S, Uske A, Regli L. Intraarterial nimodipine for the treatment of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage: a preliminary study. Neurology India. 2011 Nov-Dec. 59(6):810-816.

15. **Diehl DL, Jain AK**, Greenwald BD. Pneumoperitoneum after esophageal cryoablation in a patient with a PEG. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2011 Jun. 21(3):e141-e142.

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30. Huang Y, **Cavanaugh A, Breitwieser GE**. Regulation of stability and trafficking of calcium-sensing receptors by pharmacologic chaperones. Advances in Pharmacology. 2011. 62:143-173.

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34. **Komar M, Smith R**, Patten E. Gastroenterologists and accountable care organizations. Gastrointestinal Endoscopy Clinics of North America. 2012 Jan. 22(1):39-49.

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44. **Moreno De Luca A, Ledbetter DH**, Martin CL. Genomic insights into the causes and classification of cerebral palsies. The Lancet Neurology, Epub Jan. 18, 2012.

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48. Novack V, Pencina M, Cohen DJ, Kleiman NS, Yen CH, Saucedo JF, **Berger PB**, Cutlip DE. Troponin criteria for myocardial infarction after percutaneous coronary intervention. Annals of Internal Medicine. 2012 Feb 27. E1-E8.

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An Introduction

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This issue introduces new members of the neuroscience research team—Atom Sarkar, MD, PhD and Jonathan Slotkin, MD—and highlights the recent research accomplishments and ongoing efforts of a number of Geisinger researchers and physicians, including but not limited to:

- Frank Gilliam, MD, and Janet Robishaw, PhD, seeking new therapeutic targets for epilepsy
- Gregory James Moore, MD, PhD, the recipient of the Abigail Geisinger Clinician Investigator designation, conducting groundbreaking neuro-imaging research
- Nikolaos Tapinos, MD, PhD, improving the understanding of how traumatic brain injuries affect the peripheral nervous system
- Steven A. Toms, MD, MPH, FACS, an outstanding leader in neurosurgery and actively recruiting a cadre of clinician scientists to develop what will be an outstanding research program.

The goal of all of these projects is enhanced diagnostics, new treatments, and advances in patient management, resulting in increased quality and improvements in patient care and patient outcomes.

Interested in Neuroscience Research? Join us at the Neuroscience Interest Group and/or the Autism Research Group. Contact: Richard Fogaley at 570.214.4887.

Recent Awards

This list includes new awards and competitive renewals from external agencies and Geisinger's Clinic Research Fund from December 2011 through March 2012. To protect sponsors' confidential information, we omit dollar amounts for clinical trials and industry-sponsored agreements and some clinical trial listings. If an award is inadvertently overlooked, please forward the information to Richard Fogaley (rafogaley@geisinger.edu) for inclusion in the next issue.

Androniki Bili, MD
Rheumatology
Validation of the American College of Rheumatology 2010 Rheumatoid Arthritis Classification Criteria in the Geisinger Health System Arthritis Database
Clinic Research Fund
$19,481

Joseph A. Boscarino, PhD, MPH
Center for Health Research
Chronic Hepatitis Cohort Study (CHeCS)
CDC Foundation, Atlanta GA
$274,105

Edward Gorak, DO
Oncology
An Open-label, Randomized, Phase 3 Study of Inotuzumab Ozogamicin Administered in Combination With Rituximab Compared to Defined Investigator's Choice Therapy in Subjects With Relapsed or Refractory CD22-Positive Aggressive Non-Hodgkin Lymphoma Who are Not Candidates for Intensive High-Dose Chemotherapy
Pfizer

John Hodgson, MD
Cardiology
Evaluation of Xience Prime™ or Xience V® Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization
Abbott Vascular

Anne Moon, MD, PhD
Weis Center for Research
Novel tools for detecting FGF8 for developmental biology research
NIH
$86,443

Margaret Rukstalis, MD
Center for Health Research
The Patient-Centered Diabetes Outcomes: Pilot Study
University of Southern California/National Institutes of Health
$9,999

Evan J. Ryer, MD
Vascular Surgery
Epigenomics of Abdominal Aortic Aneurysms
Clinic Research Fund
$94,992

Steven Steinhubl, MD
Neurosurgery
Cardiovascular outcomes study to evaluate the potential of aleglitazar to reduce cardiovascular risk in patients with a recent acute coronary syndrome (ACS) event and type 2 diabetes mellitus (T2D)
Hoffman-La Roche

James Walker, MD
Chief Medical Information Officer
Automated online dispute resolution and error correction technologies for EHR
University of Chicago (Department of Health and Human Services, Office of National Coordinator)
$33,861

David Withers, MD
Psychiatry
National Infrastructure for Translating Addiction Research Into Practice
University of Buffalo/National Institutes of Health
$33,750

Wannian Yang, PhD
Weis Center for Research
Susceptibility to Statin-Induced Cytotoxicity in Breast Cancer Cells
Clinic Research Fund
$80,000

Geisinger Clinical Research

With the recent appointment of Peter Berger, MD, as director of Cardiology and co-director of the Geisinger Heart and Vascular Institute, some changes will be made to clinical research at Geisinger.

The staff of the current Center for Clinical Studies (CSS) have transferred to the Cardiovascular Center for Clinical Research. Clinicians who have studies being supported by former CCS staff will continue to be supported.

Clinicians who are initiating studies and desire assistance with the budgeting and contracting process, development of a protocol or with study management, please contact Deb Henninger, RN at dhenninger@geisinger.edu. Ms. Henninger, associate director of the Office of Research Compliance, has agreed to serve as point person.

David Ledbetter, PhD, executive vice president and chief scientific officer, will review the clinical research needs and determine the best ways to support them in the future. He plans to work with the Geisinger community as a new infrastructure for study support is developed.