JOHNS HOPKINS
# NeuroLogic

NEWS FOR PHYSICIANS FROM THE JOHNS HOPKINS DEPARTMENTS OF NEUROLOGY AND NEUROSURGERY

SUMMER 2016

JOHNS HOPKINS MEDICINE

# The Art and Science of Pediatric Neurosurgery

## Alan Cohen joins Johns Hopkins as head of division.

"WITH ADVANCES IN OPTICS, MINIATURIZATION AND COMPUTERIZED GUIDANCE SYSTEMS, WE CAN GET TO DIFFICULT AREAS MORE SAFELY, WITH LESS MANIPULATION OF THE BRAIN."

ALAN COHEN

**Alan Cohen**, new director of the Johns Hopkins Division of Pediatric Neurosurgery, recently gave the Presidential Address at the American Society of Pediatric Neurosurgeons annual meeting about the art of healing, which he condensed into three H's: humility, humanity and humor. Throughout his career, he has tried to focus not only on treating the disease but also healing the child. This includes the empathetic care he tries to deliver to his patients and their families as well as donning sequined jackets and pants to sing karaoke with his patients as his alter ego, "Dr. Elvis."

But along with the art of healing, he is also extremely focused on its science. In addition to furthering the excellent clinical care and training that has made the division among the best in the country, Cohen—who joins the division this spring along with his wife and fellow pediatric neurosurgeon, **Shenandoah Robinson**—plans to bring in new technologies that he and others have developed to make neurosurgery safer, particularly for the youngest patients.

One of these advances is three-dimensional printing. By creating models based on a patient's own unique anatomy, Cohen says, surgeons can practice the procedures before the real surgery, where the stakes are much higher.

"Models enable surgeons to see the three-dimensional relationships among the blood vessels, cranial nerves and other neural structures to find the best possible approach," he explains. "It's like a batter taking a practice swing. By practicing the surgery before going into the operating room, we can make the procedure safer."

Three-dimensional models will also revolutionize training for residents and fellows, he adds. Because of duty hour restrictions, trainees have less time to learn. But they still need to gain the same experience, and practicing on realistic models can help fill the learning gap.

Another area that Cohen hopes to focus on in his new role is minimally invasive surgery. As chief of pediatric neurosurgery at Rainbow Babies in Cleveland, and then at Boston Children's Hospital, he developed a minimally invasive surgery research program, creating new techniques and microsurgical tools that allow significantly smaller exposures to access areas deep in the brain.

"With advances in optics, miniaturization and computerized guidance systems, we can get to difficult areas more safely, with less manipulation of the brain," he says. "In many cases, that can reduce the morbidity and the potential for complications."

In addition to launching a new minimally invasive surgery laboratory in Johns Hopkins' Carnegie Building, Cohen says he's looking forward to building on the collegial and multidisciplinary care approach already in place, working with experts in pediatric neurology, orthopaedics, oncology, physical medicine and rehabilitation, and other areas.

"Working as a team enables us to do far more than anyone could do individually," he says. "The sum is greater than any of the individual parts." ■

To refer a patient, call 410-955-7337.
International inquiries: +1-410-502-7683

EPILEPSY

# Treating Epilepsy with a Laser Focus

Patients who don't respond to multiple medications for epilepsy often face a painful catch-22—either continue to suffer from debilitating and dangerous seizures while hoping to be one of the rare minority who will eventually benefit from further medications, or undergo surgery to remove the seizure focus, a procedure that typically involves an open craniotomy and comes with inherent risks, including the chance of deficits to speech, memory, vision, motor or sensory function.

"It's not surprising that only about 5 percent of patients with intractable epilepsy undergo surgery annually," says Johns Hopkins epileptologist **Joon Kang**. "This procedure is probably underutilized because patients are afraid of mortality or permanent morbidity from complications."

However, a third option now available at Johns Hopkins could make epilepsy surgery more palatable to the thousands of patients who could benefit from it: a procedure known as laser interstitial thermal therapy, or LITT. Johns Hopkins is currently the only hospital in Maryland and the Washington, D.C., area that offers this operation, joining a handful of other medical institutions across the country.

LITT, which has been approved by the U.S. Food and Drug Administration for other conditions since 2007 but has only been used for epilepsy in the past four years, involves threading a wire holding a laser applicator through a small skin incision and small hole in the skull into the brain. Using MRI guidance to precisely locate the seizure focus, surgeons, including Johns Hopkins neurosurgeon **William Anderson**, heat the affected tissue with the laser to temperatures that permanently destroy it. The risk of damage to nearby tissues is low because the surrounding cerebrospinal fluid wicks heat away.

**Epileptologist Joon Kang and neurosurgeon William Anderson—both pictured at right—are among the handful of practitioners in the nation using laser interstitial thermal therapy to treat epilepsy. The minimally invasive procedure, performed by surgeons using MRI guidance, involves threading a wire holding a laser applicator through a small skin incision and a small hole in the skull into the brain. Above, Anderson and on-site tech support Bryan Molter review a case.**

"It's an extremely targeted approach," Anderson says.

This focused procedure has a number of benefits, he adds. Because it's minimally invasive, patients avoid the large, visible scar, potentially deformed skull, severe postoperative pain and long recovery times that typically accompany the traditional open surgery. LITT's surgical wound is typically closed by a stitch or two, and most patients spend just a single night in the hospital. They're able to return to their normal activities within a week, compared to the four to six weeks most patients need to recover from a craniotomy. And because the procedure is so targeted, Anderson says, the risk of functional and cognitive deficits drops significantly.

Compared to the open procedure, LITT has a slightly lower success rate, caution Kang and Anderson—about 50 to 60 percent become free of disabling seizures, compared to 60 to 70 percent of patients undergoing traditional surgery. However, they say, experience amassed by centers offering LITT is gradually improving this procedure. Additionally, patients who have LITT can still undergo an open procedure if the minimally invasive one isn't successful.

"We're very excited to be able to offer this new procedure," Anderson says. "It's a paradigm shift in how we treat epileptic patients." ■

To refer a patient to the Johns Hopkins Epilepsy Center, call 410-955-9441.
International inquiries: +1-410-502-7683

PRENATAL DISORDERS

# Modeling Prematurity

## Research models point to prenatal insults responsible for certain injuries and open possiblities for treatments.

Faced with the choice of any specialty during her medical training, **Shenandoah "Dody" Robinson** decided to pursue neurosurgery because it was the one most closely associated with what it means to be human. "It's tremendously rewarding and a real privilege to be able to help people optimize their ability to communicate and move, all by using surgical techniques," she says.

Working with children is an additional honor, she adds. After meeting her young patients in the clinic, hospital or even neonatal intensive care unit, she often follows them throughout their development. Consequently, maximizing their outcome doesn't mean just getting them through to the other side of an acute illness, she says—it's more about giving them the best chances to succeed as they grow. In her clinical practice,

# A SMART Approach to SMA Research

**Neurologist Charlotte Sumner receives support from the Spinal Muscular Atrophy Research Team for her research on the neuromuscular disease.**

When Tim and Gretchen Reilly's son, Matthew, was diagnosed with spinal muscular atrophy (SMA) type 2 a decade ago, the family spent the next year adjusting to a new normal. Then, they turned to action.

Because this genetic neuromuscular disease is relatively rare—affecting just one in every 6,000 to 10,000—and is fatal in its most common and severe form known as type 1 within the first two years of life, relatively few research dollars are devoted to developing treatments for children like Matthew, now 11, who will live with severe and progressive muscle weakness. Very informally, the family began fundraising for the largest SMA research organizations. But eventually, Tim says, they wanted to do something "a little different."

As a scientist who currently leads immuno-oncology early drug development for a large pharmaceutical company, he's seen firsthand how most biomedical research gets funded: Whether at governmental funding organizations like the National Institutes of Health or biopharmaceutical companies, most funders want to invest only in research that's headed in a proven direction and is likely to succeed. But that's not where many truly groundbreaking advances come from, Tim explains.

"Harebrained, out-of-the-box ideas have led to some of the most amazing discoveries we have in our culture," he says.

Finding a way to fund such risky research could dramatically change the research landscape for SMA, Tim and Gretchen reasoned. That's why the couple, along with friends and family members back in their hometown of Buffalo, New York, started the Spinal Muscular Atrophy Research Team (SMART; www.smarthope.com) in 2009. Their goal was to fund creative scientists doing work related to SMA who had the same mindset and passion to explore ideas outside the mainstream.

They found their match with **Charlotte Sumner**, a Johns Hopkins neurologist who has made SMA the cornerstone of her laboratory research. For the past five years, SMART, including its foundational supporters like the Buffalo Firefighters Local 282 and Buffalo Sabres organization, has funded Sumner's investigation with yearly grants between $100,000 and $150,000.

For decades, researchers have known that the disease stems from a defect in a gene known as survival motor neuron 1 (SMN1), which causes motor neurons to ultimately die from a lack of the protein produced by this gene. This deficiency can be partly ameliorated with functional proteins from another gene known as SMN2, which varies in copy number from person to person. Consequently, the type and severity of a patient's disease correlates to the number of SMN2 copies encoded in their genome and the corresponding amount of protein they produce. However, the SMN2-derived protein doesn't compensate completely for SMN1.

The vast majority of the field is focused on trying to change SMN2's assembly so that it better matches the function of SMN1, and drugs for this purpose are being tested in clinical trials. But even then, explains Sumner, patients will still only have as much SMN2 protein as their gene copy number provides.

One of her "harebrained ideas" that's been funded by SMART has focused on finding unique ways to encourage cells to increase the amount of SMN2-derived protein that they make. In the past three years, Sumner and her colleagues have identified a set of noncoding RNAs—genetic code that doesn't direct protein production but has a regulatory role on other genes—that appears to be responsible for deciding the amount of SMN2-derived protein produced. These noncoding RNAs could be key for developing a therapy that could be used in conjunction with those already in development to make SMN2-derived protein a better match for SMN1, both boosting and bettering SMN2-derived protein in SMA patients.

In work also funded by SMART, Sumner identified a window when motor neurons affected by this disease stop working well but are still alive. This period could represent a critical time to deliver therapies.

Rather than spend hours on lengthy proposals that most funding organizations require, Tim asks Sumner simply to write up a quick summary and a list of her most out-of-the-box ideas, which they discuss and fine-tune over the phone. This

*(continued on back page)*

Robinson specializes in the surgical treatment of epilepsy and spasticity. These disorders often arise from early events that impact development and affect all aspects of a child's life, including socialization, education and family interactions.

As a new member of the Johns Hopkins Department of Neurosurgery faculty, in addition to her clinical skills, Robinson will be bringing with her the long-running research program she's developed to understand how to optimize the recovery of the developing brain after early insults. Toward that goal, she and her colleagues have developed several animal models to recapitulate prenatal injury that can lead to epilepsy, spasticity and related disorders. Recently, the team reported a model that replicates many of the deficits seen in children with encephalopathy of prematurity, an umbrella term that encompasses central nervous system abnormalities associated with preterm birth. By inducing transient systemic hypoxia-ischemia through uterine artery occlusion and placental inflammation with intra-amniotic lipopolysaccharide injections midgestation, the researchers found that the resulting offspring displayed central nervous system damage with characteristic white matter, gait and imaging abnormalities reminiscent of children born extremely preterm.

This and other models the team works with have allowed them to gain insight into which prenatal insults are responsible for various injuries and also what treatments might be effective in alleviating them. For example, numerous studies led by Robinson have shown that erythropoietin, the glycoprotein hormone responsible for red blood cell production, also has a neuroprotective function, supporting the genesis, survival and differentiation of neurons and oligodendrocytes. Although this hormone is already in phase III clinical trials for infants born before 28 weeks gestation, it's unclear which other neonates and infants might benefit from its use and how dosing needs to be tailored to particular conditions. Robinson and her team are currently trying to answer these questions in the lab.

Robinson collaborates with a variety of specialists, including pediatric neurologists, developmental pediatricians, orthopaedic surgeons and others, and hopes that her research findings will help each child achieve his or her best long-term outcome. "Maximizing the child's comfort, independence and function," she says, "is our primary goal." ■

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## A SMART Approach to SMA Research

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unusual system allows her make the most of her time and mental energy in the lab.

"It's very unconventional," says Sumner, "but Tim trusts that this money is going to good use."

Focusing resources on research, adds Tim, is the best way to accomplish SMART's goal: to help patients like Matthew to eventually convert SMA to more of a chronic condition that can be managed rather than a life-threatening disease and, someday, to find a cure. ■

To refer a patient with SMA, call 410-955-4259. International inquiries: +1-410-502-7683


**Matthew Reilly receives a hockey stick from a player on the Buffalo Sabers, an organization that is one of the Spinal Muscular Atrophy Research Team's biggest proponents.**

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