

**Johns Hopkins  
Neurology &  
Neurosurgery**

# Doorways to Discovery

## inside

- 2 Battling Brain Tumors
- 4 Improving Cancer Outcomes
- 6 Rethinking Alzheimer's
- 8 Reversing Dementia
- 10 Revolution in Stroke Recovery
- 12 Preventing Pain
- 14 New Hope for SMA
- 16 The Right Menu for Epilepsy
- 18 Speeding Drug Discovery

## mission

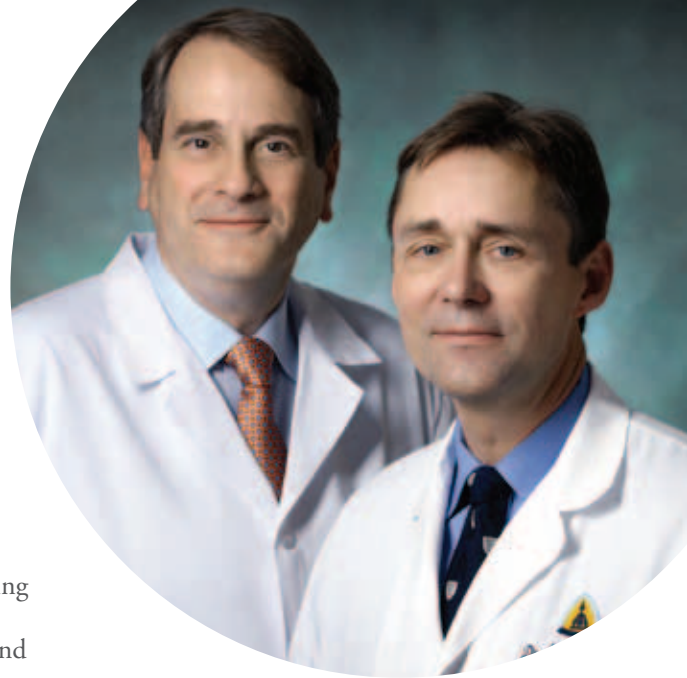
The mission of Johns Hopkins Medicine is to improve the health of the community and the world by setting the standard of excellence in medical education, research and clinical care. Diverse and inclusive, Johns Hopkins Medicine educates medical students, scientists, health care professionals and the public; conducts biomedical research; and provides patient-centered medicine to prevent, diagnose and treat human illness.

## vision

Johns Hopkins Medicine pushes the boundaries of discovery, transforms health care, advances medical education and creates hope for humanity. Together, we will deliver the promise of medicine.

## core values

Excellence & Discovery  
Leadership & Integrity  
Diversity & Inclusion  
Respect & Collegiality



## From the Directors

Advances in neurology and neurosurgery are unfolding here at Johns Hopkins at a breathtaking pace, and we're excited to share some of our most significant breakthroughs in patient care and translational research in the pages that follow.

Neurosurgeon Chetan Bettegowda, for example, is at the forefront of developing a DNA-based “liquid biopsy” for brain cancer, using cerebrospinal fluid and blood, which could spare patients from undergoing surgical biopsy. Meanwhile, researchers such as neurosurgeon Daniele Rigamonti are pushing to dramatically improve quality of life for their patients. He has developed a tool to better ascertain which patients exhibiting dementia symptoms could have their condition reversed through surgery for normal pressure hydrocephalus.

Ever aware of the daunting complexity of the nervous system and its often-devastating disorders, our researchers are serious and single-minded in their quest for answers. But that doesn't mean there's no room for fun. Just ask Tom Crawford, who makes sure his young patients with spinal muscular atrophy have a blast when they come to have their muscle strength tested. Or visit the lab of John Krakauer, where he and his team have developed an immersive new video game, starring Bandit the dolphin, which could change the model for rehabilitation after stroke.

Thanks to imaginative researchers like these and the others you'll learn more about here, we've never been more optimistic about the future for our patients with neuro-related disorders. We hope you'll share our optimism—and excitement.

**Henry Brem, M.D.**  
Director of Neurosurgery  
Harvey Cushing Professor of Neurosurgery  
Professor of Oncology, Ophthalmology  
and Biomedical Engineering

**Justin C. McArthur, M.B.B.S., M.P.H.**  
Director of Neurology  
Professor of Neurology, Pathology,  
Medicine and Epidemiology

# Surprise Finding Yields a Possible Tumor-Fighting Drug

A serendipitous finding in lab mice made by research professor **Gregory Riggins** and neurosurgeon **Gary Gallia** is creating excitement as a possible treatment for glioblastoma, an aggressive brain tumor.

Riggins' lab is known for discovering cancer-causing gene mutations and for assessing new drugs at the preclinical phase. Ordinarily, he and his colleagues have no trouble triggering glioblastoma cells to proliferate in mice. But over the course of several months in 2009, they encountered one group of mice in which the tumors would not grow. After some investigating, the scientists discovered that the mice had been treated with the veterinary antiparasitic drug fenbendazole.

Searching the literature, they found reports that fenbendazole had been shown to inhibit cancer growth. Then,

by trial and error, they determined that the related drug mebendazole—which has been used for the last 60 years to treat parasites in the human gastrointestinal tract—might also hold potential for stalling glioblastoma.

"We screened a lot of drugs in this family of compounds, and it was mebendazole that worked best," says Gallia. "This is what we'd been looking for."

With that, Riggins, Gallia and their research team launched a program to understand the drug, improve its effectiveness against glioblastoma cells and have it manufactured for testing in patients. "The drug company that previously supplied mebendazole in the U.S. was no longer manufacturing it," says Riggins, adding that they finally found a company in India that could supply the quantities they'd need for a clinical study. The scientists believe the

drug helps obstruct tumors by inhibiting formation of strands of tubulin—proteins needed by cancer cells to grow.

Glioblastoma is a fast-moving cancer. "Average survival is 15 to 20 months," says Riggins. "We're trying to improve therapy as quickly and strategically as we can." The Johns Hopkins team is at a critical juncture now—a phase I clinical trial with 24 patients to determine the drug's safety. "We are using the highest dose allowed by the review boards of Johns Hopkins and the Food and Drug Administration, and patients are tolerating it well," Riggins says of the study, which is about 50 percent complete.

"At best, the drug will slow tumor growth," says Riggins. He and his team are looking to pair it with other drugs. They expect that their formulation of mebendazole will also work in pediatric cases. ●

## A Liquid Biopsy to Track Cancer and Avoid

Today's big advances in medicine are built on a foundation of past discoveries, new technologies and forward thinking. At the Ludwig Center at Johns Hopkins, all the parts are coalescing into major gains for diagnosing and controlling cancer. The latest is a liquid biopsy, "a noninvasive way of monitoring a person's cancer status," typically by using

the patient's blood, explains Johns Hopkins neurosurgeon **Chetan Bettegowda**.

"Our research is focused on understanding the genetic makeup of a tumor. Once we know it, we can search for a particular DNA biomarker in a patient's blood and use that signature to quantify the cancer, decide on the best treatment, and monitor the patient over time for

drug resistance and other responses," he says.

The liquid biopsy concept has been around for more than a decade, but until now, clinicians have largely relied on protein biomarkers rather than DNA biomarkers, which have many potential applications. For example, researchers showed about 10 years ago that several cancers, including malignant

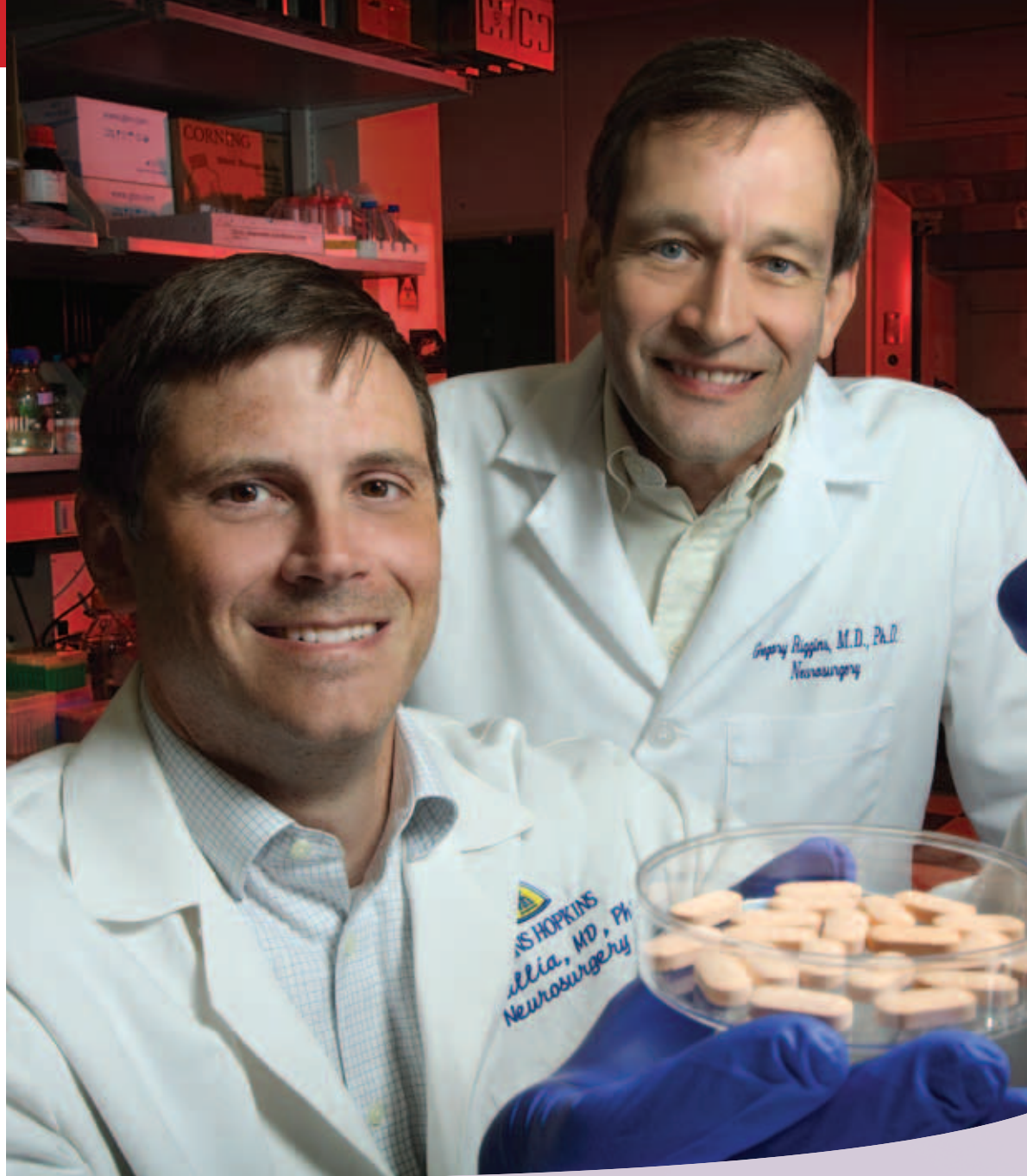
melanoma, contain a faulty version of a protein called B-Raf. Drugs were developed to inhibit the mutant B-Raf. "That was a big step forward," says Bettegowda. "But tumors almost always will find a way to become resistant to the drug. Having a liquid biopsy can help detect the resistance that is forming and allow physicians to change treatment in real time."

○ **Challenge:** To find an effective drug to combat glioblastoma, an aggressive brain tumor.

○ **Approach:** Riggins and Gallia are using mebendazole, a drug in the family of compounds that includes fenbendazole, a veterinary antiparasitic that had serendipitously been discovered to prevent tumor growth in lab mice.

○ **Progress:** A phase I clinical trial of mebendazole, involving 24 patients, is currently underway.

Gallia, left, and Riggins found what they'd been looking for with mebendazole.



## Surgery

As a neurosurgeon, Bettgowda is focused on a unique aspect of a liquid biopsy for brain cancers. “Brain cancers do not shed much DNA into the blood, probably because of the natural blood-brain barrier,” he explains. The Ludwig Center researchers and worldwide collaborators are working to detect brain cancers in cerebrospinal fluid (CSF) instead, via a spinal tap.

Bettgowda wants to avoid surgical procedures whenever possible. He envisions, for example, using a CSF liquid biopsy for brain tumor patients who develop treatment side effects that mimic tumor progression. “We’d spare the patient going into surgery for a biopsy of the tumor itself.”

The researchers haven’t completely ruled out a

blood-based liquid biopsy for analyzing brain tumors and responses to treatment. Blood- and CSF-based liquid biopsies are being researched in parallel. “We expect to develop new ways of detecting molecules of DNA from nervous system cancers that could show up in blood,” says Bettgowda. ●

○ **Challenge:** To accurately track whether brain tumors are growing or receding without resorting to surgical biopsy.

○ **Approach:** Bettgowda is testing a “liquid” biopsy, using body fluid.

○ **Progress:** Tests are being developed to track cancer-specific DNA in cerebrospinal fluid and blood.

# Spinal Tumor Surgery: Eliminating the Gray Area

A cancer surgeon strives to give patients the gift of hope, tempered by honesty, and **Daniel Sciubba** is pushing to give patients a more accurate idea of what they can expect after surgery. “A realistic prognosis impacts patients’ decision-making and quality of life,” says Sciubba, who looks at preoperative factors that contribute to postsurgical survival.

Sciubba specializes in the surgical treatment of spinal tumors. To

study outcomes related to surgery of metastatic cancers of the spine, he and his fellow researchers consider factors like the type of tumor, age of the patient, nature of the surgical procedure, adjuvant therapies and possible complications.

The scientists discovered, for example, that breast cancer patients with spinal metastases had better postsurgical survival if their cancer was hormone receptor-positive (dependent on estrogen and/or progesterone for its growth), that postsurgical survival of patients with prostate metastases is also hormone-dependent, and that en bloc resection of a spinal sarcoma—removal of the main tumor and surrounding portions of the spinal column—confers a survival advantage over intralesional resection, a more modest approach.

“The goal of a surgeon, to my mind, is to be able to tell patients the reality of their options,” says Sciubba. “We don’t have a crystal ball, but our data are enabling us to say to the patients, with added confidence, that if you choose this path, the likely outcome is X, versus this path, where the likely outcome is Y.”

Over time, Sciubba and his colleagues are getting better at predicting outcomes, based

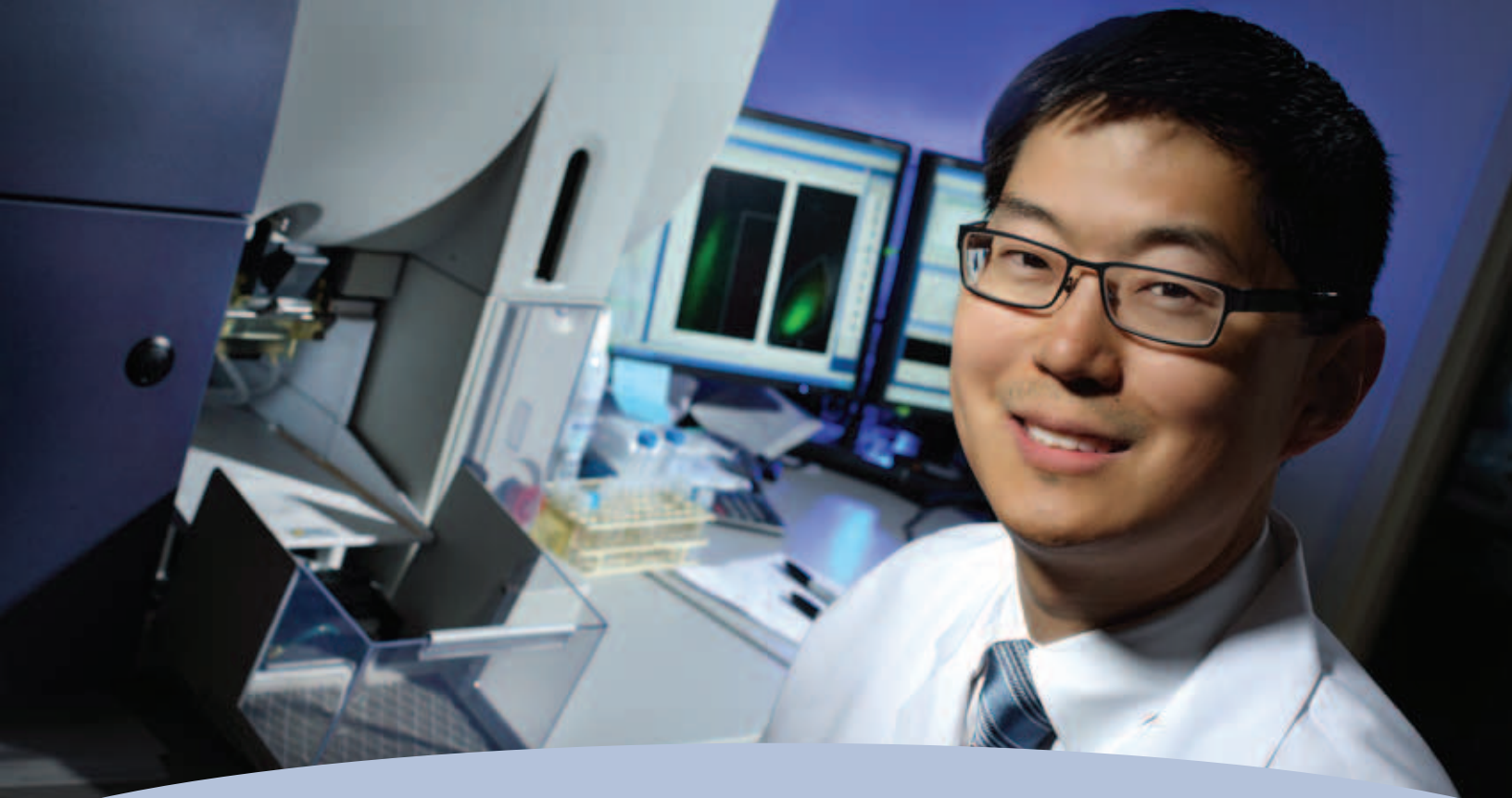
on experience and data from many sources. “We are finding more and more granular ways to predict surgical outcomes that go beyond the usual,” he says. Smoking, arthritis, osteoporosis, amount of pain and scoliosis are just a few critical factors to consider. “If we have 10 things that we can use to predict good or poor outcomes, we eliminate as much of the gray area as possible, and the patient can make an informed decision.” By this, he means whether to undertake the surgery, and even which surgery is the best choice, given the best available information. ●

○ **Challenge:** To provide patients with a more accurate idea of what to expect from spinal tumor surgery to help them in decision-making.

○ **Approach:** Sciubba is undertaking large-scale studies to link surgical approaches and patient characteristics to survival following spinal tumor surgery.

○ **Progress:** Based on the research data, Sciubba and his colleagues are increasingly better able to advise patients on their options and outcomes.





## Delivering a One-Two Punch to Cancer

At Johns Hopkins, questions that arise in the clinic become targets for research, and findings from research circle back into potential treatments for new patients. That's exactly how neurosurgeon **Michael Lim**'s latest clinical trial got started.

While caring for patients with melanoma that metastasized to the brain, Lim noticed that a subset of brain tumors that were irradiated developed a robust inflammation in this area.

At the time, he was also studying a family of cancer drugs known as checkpoint inhibitors. This class of immunotherapies targets

molecules on the surfaces of cancer cells that effectively shut off the body's immune response, allowing these cells to evade death and proliferate unchecked. Two particular checkpoint inhibitors, anti-bodies against the proteins PD-1 and CTLA-4, have shown promise in helping extend survival for several different types of cancers. However, neither of them alone has proven to be a cure.

Because the inflammation Lim saw in the clinic indicated an immune response, he wondered whether combining radiation with one of the checkpoint inhibitors might deliver a one-two punch to

patients' cancers, providing a more effective therapy than either modality on its own.

To test his idea, he looked at a mouse model of glioblastoma. Exposing the mice to radiation and to PD-1 produced a significant number of long-term survivors—mice whose cancer never reappeared. More remarkable, when Lim and his colleagues reinjected the treated animals with tumor cells, they remained cancer-free. "It showed us that their immune system was now trained to kill cancer," he says.

Since antibodies against CTLA-4 are FDA-approved to treat melanoma but anti-

bodies against PD-1 aren't yet, Lim and his colleagues repeated the experiment using CTLA-4 in a mouse model of metastatic melanoma. These results were similarly exciting—so promising that Lim and his colleagues recently opened a clinical trial to test the effects of this combination in patients with metastatic melanoma. ●

○ **Challenge:** To find a more effective treatment for aggressive cancer.

○ **Approach:** By combining radiation with specific immunotherapies, researchers deliver a one-two punch that is more effective than either modality on its own.

○ **Progress:** Lim and colleagues have launched a clinical trial in patients with metastatic melanoma.

**In a separate clinical trial**, this one involving patients with advanced melanoma that has metastasized, Michael Lim is also taking a one-two punch approach. This time he's using a drug called ipilimumab—which targets the immune system—and is teaming it with stereotactic radiosurgery, a precise type of radiation therapy. The experimental treatment, delivered over the course of two months, builds on research that has shown that radiation therapy may prime tumors to respond to subsequent immunotherapy.

# A Stimulating Approach to Alzheimer's

**S**everal years ago, doctors in Toronto set out to quell the appetite of an extremely obese patient by electrically stimulating his brain's appetite center via deep brain stimulation (DBS). A surprise effect—DBS elicited old and vivid memories—has given rise to a new strategy for slowing cognitive decline in people with Alzheimer's disease.

DBS is now being tested in 42 patients with early-stage Alzheimer's disease in a clinical trial at Johns Hopkins and six other leading North American research centers. The ADvance Study is led by psychiatrist **Constantine Lyketsos**, director of the Johns Hopkins Memory and Alzheimer's Treatment Center, and neurosurgeon Andres Lozano of the University of Toronto. Preliminary studies carried out in Toronto suggest that stimulating the hippocampal fornix—the brain's memory center—can release memories of specific events and also improve the brain's

use of glucose, which is significantly reduced in early stages of Alzheimer's.

"An Alzheimer's disease pandemic is inevitable, and we need new therapies if people are to retain a good quality of life," says Lyketsos. According to the Alzheimer's Association, more than 5 million Americans currently suffer from Alzheimer's, and that number is expected to reach 16 million by the year 2050.

**William Anderson** is the Johns Hopkins neurosurgeon who performs the delicate DBS operation, which he'd previously done hundreds of times in patients with Parkinson's disease to calm their tremors. "But this was a slightly different operation," he explains. "To reach the fornix, the wires had to traverse the tough walls of the brain's fluid-filled ventricles, which sometimes resist passage."

Patients undergoing DBS carry a pacemakerlike stimulator implanted just

under the skin. An electrode extends from it, painlessly, to the brain. Half of the patients in the ADvance Study had the DBS devices activated two weeks after surgery, while the remainder will have the device turned on after one year. All will be regularly assessed for at least 24 months to measure their rate of Alzheimer's progression.

"The study participants have very mild dementia," says Lyketsos. "We want to be able to attenuate their disease process so that fewer ever get to the more advanced stages." The researchers expect to have their answers in 2015. If the study's outcome supports the safety of DBS in Alzheimer's patients and suggests some efficacy, researchers will undertake a new set of studies to test optimal rates, dose of stimulation and placement of wires, since the electrode has multiple tips that can be turned on in various combinations. ●




## Changing the Future of Aging

**A**lzheimer's disease doesn't arise suddenly. It begins years earlier as the brain starts accumulating two proteins: amyloid protein that forms plaques and tau protein that forms tangles. Ultimately, related to damage from these proteins, brain cells die, brain regions responsible for memory and cognition shrink, and symptoms of dementia emerge.

Cognitive neuroscientist **Marilyn Albert** and her collaborators measure these proteins in cerebrospinal fluid

(CSF), use sophisticated MRI brain imaging techniques to study affected brain regions, and draw parallels between their findings and the progression of cognitive decline.

Most recently, she and colleagues at Johns Hopkins studied several hundred people, most of whom were first evaluated when they were middle-aged and symptom-free. About one-fifth have progressed to mild cognitive impairment or dementia. The researchers are looking for markers in normal individuals that predict who will



Neurosurgeon  
William Anderson

○ **Challenge:** To slow Alzheimer's symptoms and the disease's spread in the brain so that fewer patients experience the most severe stages of the disease.

○ **Approach:** Deep brain stimulation (DBS)

○ **Progress:** DBS is being tested in a clinical trial at Johns Hopkins and six other leading North American research centers.

develop symptoms many years later. Why? So treatment regimens can be started at the optimal time—not too late and not too soon for the best effect. Baseline ratios of amyloid and tau in CSF, as well as measures on MRI scans, appear to be good predictors.

“We think that current drugs for Alzheimer's disease might be failing because the timing is off. And we think that the markers from CSF or from brain imaging will tell us when to start treating,” says Albert.

She is director of the Alzheimer's Disease Research Center at Johns Hopkins and of this project, known as BIOCARD. Recently re-funded by the National Institute on Aging, she and her colleagues are expanding their evaluations to include several innovative new procedures.

“When better treatments become available, combined with early diagnosis, we could help change the course of Alzheimer's and the future of aging.” ●

○ **Challenge:** To predict who will develop Alzheimer's disease and begin to treat them before it is too late.

○ **Approach:** Albert is identifying markers of Alzheimer's in its earliest stages.

○ **Progress:** Tests are showing that amyloid and tau in cerebrospinal fluid and measures on MRI scans in nonsymptomatic individuals are helpful in predicting who will develop symptoms many years later. Additional work is needed to improve the accuracy of prediction.

# A Reversible Form of Dement

.....“**R**eports indicate that as many as five out of every 100 people older than 65 who are diagnosed with Alzheimer’s disease, Parkinson’s disease, other forms of dementia or problems with balance could actually have a reversible form of cognitive and motor deterioration,” says neurosurgeon **Daniele Rigamonti**, an expert in the field of normal pressure hydrocephalus (NPH).

In NPH, the brain’s ventricles overfill with cerebrospinal fluid (CSF) because of an obstruction in the normal CSF drainage system. “The excess CSF causes the ventricles to expand and the brain to become compressed in a way that causes stereotypical signs of impairment,” he says. These signs include poor balance, a wide-based gait, attention and short-term memory problems, urinary urgency, and frequently, urinary incontinence.

If NPH were diagnosed early enough, before brain damage is permanent or extensive, a surgical intervention to shunt the CSF past the obstruction could help about 90 percent of patients with the condition, says Rigamonti, who is developing a new tool to hone the diagnosis.

When a patient is suspected of having NPH, a typical workup includes a spinal tap for draining off enough CSF to temporarily relieve the pressure on the brain. “If the symptoms decrease after the spinal tap, then we know we have a good chance of reversing the downward trend,”

Rigamonti notes. The body naturally replaces the removed CSF, starting the buildup of pressure over again.

Rigamonti believes that the best judge of improvement after the spinal tap is probably not the medical staff watching the patient walk through the clinic hallways, but rather the patient and family in their own home full of obstacles. “The tool I’m working on is a system that they can use to record their observations. We are seeing that the more certain they are of improvement, the better the surgical outcome. Our predictions for surgical success are being informed by these preoperative evaluations,” he says.

Rigamonti says that final data on the efficacy of the tool should be collected in a matter of six months. This will assist doctors in selecting the best candidates for surgery and help patients understand their chance of improvement, he notes.

Rigamonti would like more family practitioners, internists and neurologists to consider NPH in older patients who are evaluated for a fall, particularly if brain imaging suggests enlarged ventricles. “It is the only form of dementia that gets better, so there is a huge potential for improving quality of life,” he says.

Rigamonti is the editor of a comprehensive new book for medical professionals, *Adult Hydrocephalus*, and he is working on another for patients and families. ●



Ahn (left) and Pindrik

## Reducing Radiation Expos

.....“**T**he number of babies born with hydrocephalus is estimated at one to two out of every 1,000 births. While there is no cure, surgeons can relieve the damaging pressure by threading a thin catheter from the ventricles to the abdominal cavity, where ex-

cess cerebrospinal fluid is drained and absorbed.

A worry, especially for young growing bodies, is that the necessary and frequent CT scans needed to monitor the shunts carry a risk for cell damage and cancer.

ia

○ **Challenge:** To accurately diagnose normal pressure hydrocephalus (NPH) to surgically treat and improve patients' cognitive and motor skills.

○ **Approach:** Rigamonti is developing a home test to assess cognitive and motor skills improvement following removal of a small amount of cerebrospinal fluid in patients being evaluated for NPH.

○ **Progress:** The home test is being evaluated for efficacy.



## ure in Children with Hydrocephalus

A Johns Hopkins team led by neurosurgeons **Edward Ahn** and **Jonathan Pindrik**, in collaboration with **Thierry Huisman** and **Aylin Tekes** from pediatric neuroradiology and **Mahadeveappa Makesh** from imaging physics, recently developed a technique

that reduces radiation exposure without compromising diagnosis and patient care. Instead of taking the usual 32 to 40 CT “slices,” the method requires just seven slices, thus reducing X-ray exposure by more than 90 percent.

“We have been searching for ways to minimize radiation exposure in kids without sacrificing the diagnostic accuracy of the images, which is no easy feat,” says Ahn. “We believe that our limited-slice CT scans achieve that balance.” ●

# A Simulated Dolphin to Guide Stroke Recovery

**T**he term visionary thinker only begins to describe neuroscientist **John Krakauer**, who is “staging a revolution” to achieve a better future for patients with motor loss caused by a stroke. His vision involves a virtual sea mammal.

Krakauer starts with the premise that we need to expand our thinking about the physical rehabilitation potential for stroke survivors. He notes that when a rodent who has had a stroke is placed in a setting with wheels, toys and “colleagues”—as Krakauer calls the animals’ cage mates—the recovery of its brain function is remarkable compared to humans’, whose rehabilitation routine has traditionally been governed by patterned limb movement.

Rehabilitation for stroke patients should include exciting visual, cognitive and motor activities, says Krakauer, who wants to capitalize on plasticity of the human brain to help patients maximize their abilities.

“The general belief is that the window of opportunity for significant and positive improvement in patients with stroke is about three months,” notes Krakauer. He and his Johns Hopkins team have borrowed from gaming, animation, animal behavior, robotics, philosophy, engineering and more to develop

a new model for maximizing recovery within that time frame and perhaps beyond. The centerpiece of the model is a simulated dolphin—named Bandit and developed in the Brain, Learning, Animation, and Movement (BLAM) Lab—for new stroke patients to manipulate while it swims, jumps and hunts in the ocean. Krakauer’s collaborators, **Omar Ahmad**, **Promit Roy** and **Kat McNally**, designed the dolphin and the technology’s sophisticated gaming features based on long hours of studying the sea mammals at the National Aquarium in Baltimore.

The idea is to have patients control the complex acrobatics of the dolphin through flicks of their fingers, wrists and arms in a video game fashion, all the while sending streams of data back to the BLAM Lab. “It is a motivating, immersive and beautiful game,” Krakauer says.

In addition to its potential for therapy, the game, called I Am Dolphin, can be used for studies of normal learning. By analyzing data from hundreds of users, the scientists will also be able to see how increased skill in the control of this avatar changes over the hours that users play the game. The researchers will gain a wealth of information that would be nearly impossible to gather in a lab setting.

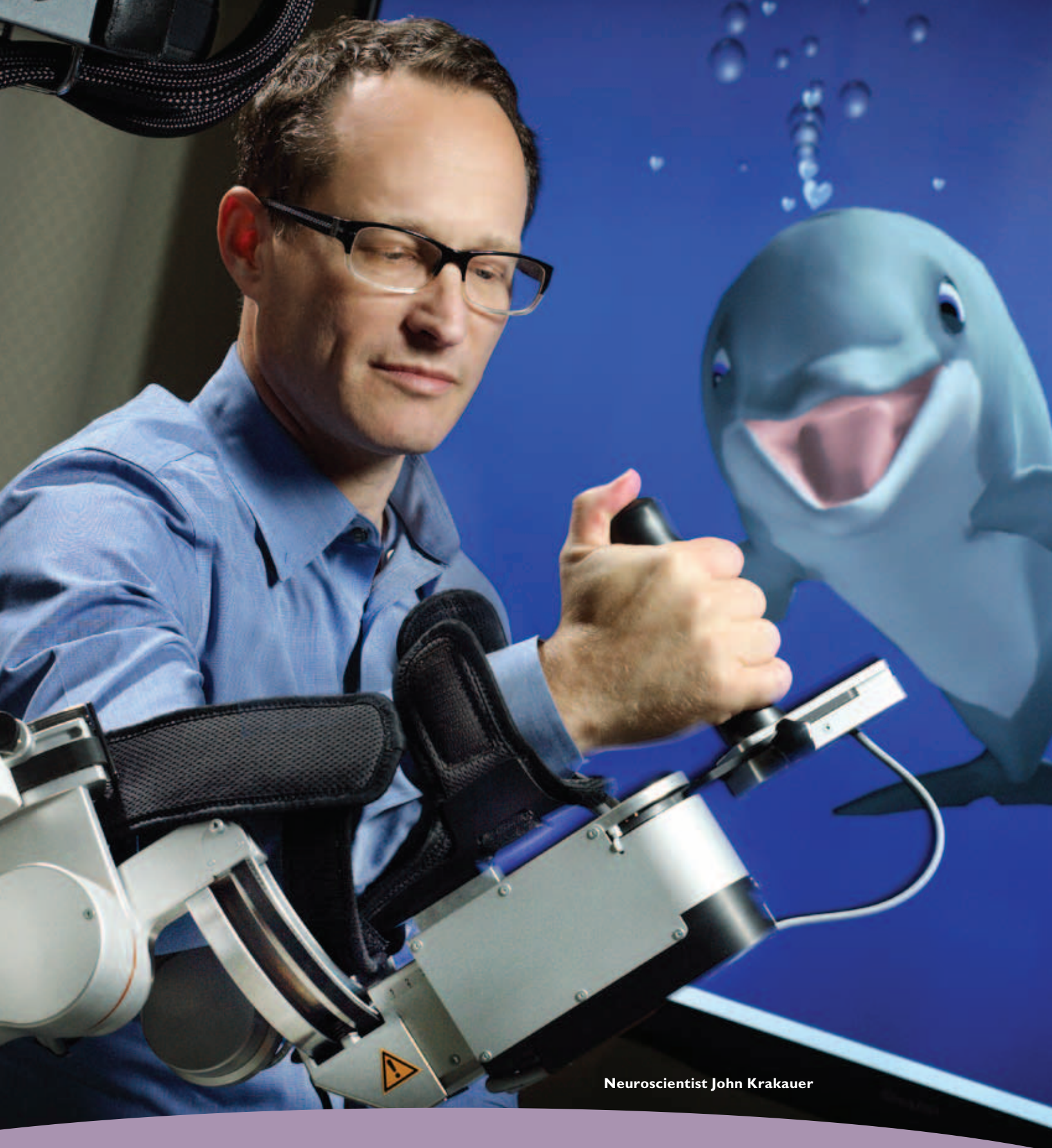
Krakauer’s team is about to launch a clinical trial involving recent stroke patients. His hope? That patients will get “lost” in being Bandit, playing as if they are frolicking dolphins. If they recover faster than patients who won’t be meeting this virtual dolphin, it could eventually shift the model for rehabilitation for patients with stroke and other neurological injuries and diseases. ●

○ **Challenge:** To design a way to improve functional capacity in stroke patients.

○ **Approach:** A team will track outcomes as recent stroke patients play a specially designed video game starring Bandit the dolphin.

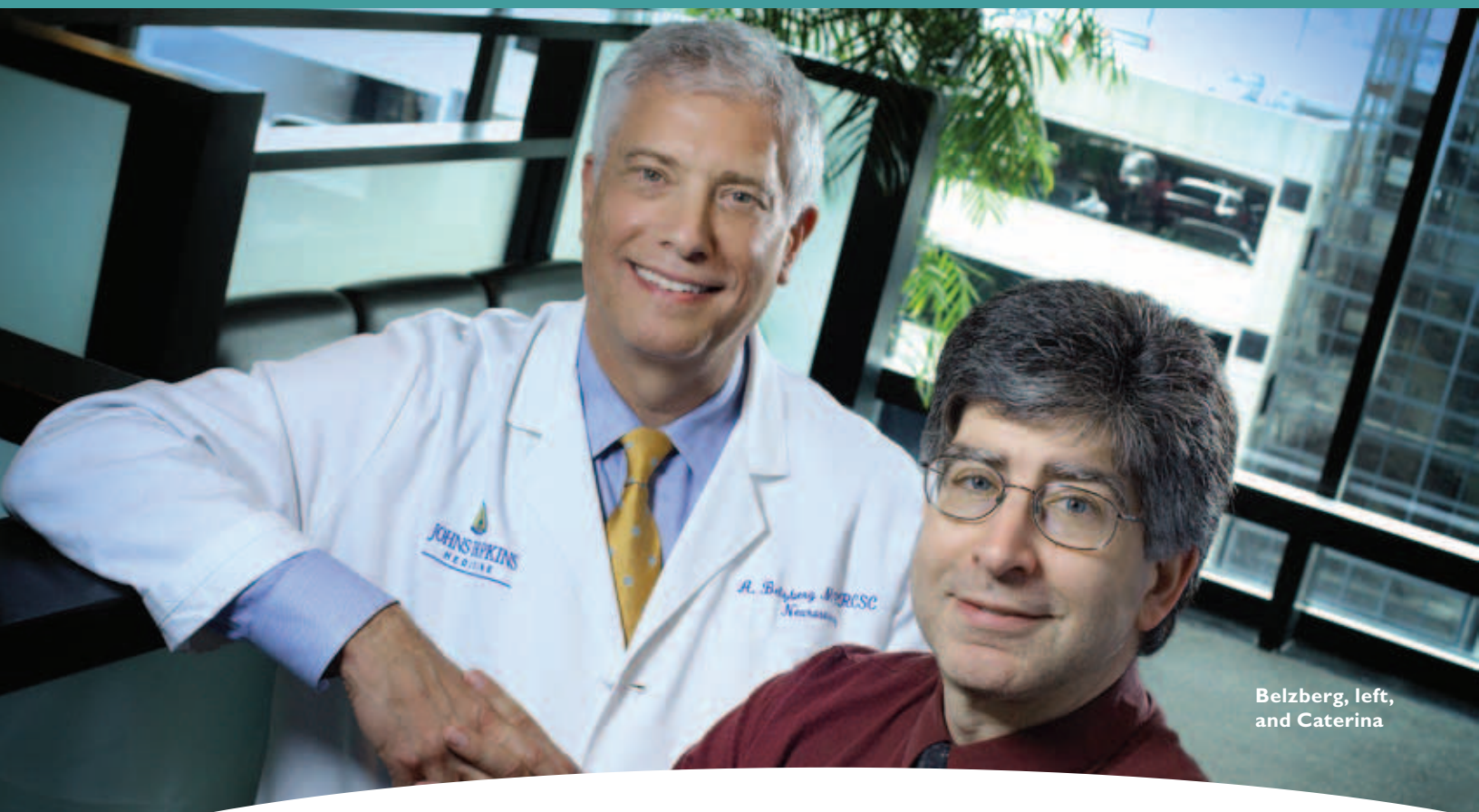
○ **Progress:** Clinical trials of the video game are beginning.





Neuroscientist John Krakauer

**The Johns Hopkins Hospital** has been designated as a Comprehensive Stroke Center by the Joint Commission and Maryland's Institute for Emergency Medical Services Systems, a distinction awarded based on the capacity to offer specialized care to the most complex stroke patients on a 24/7 basis.



Belzberg, left,  
and Caterina

# Collaborating to Control, Prevent and Eliminate Pain

**A**lthough pain serves a purpose to let us know when we have been injured, in many patients, the pain signaling system is somehow broken, resulting in chronic pain.

The Neurosurgery Pain Research Institute at Johns Hopkins was developed using a generous gift from an anonymous donor to fundamentally transform our understanding of pain and to develop new and effective strategies to treat it.

This mission is being accomplished through an unprecedented collaborative effort that brings together scientists across Johns Hopkins who study pain. Experts across diverse fields are now working in concert so that the whole is greater than the sum of its parts to achieve the institute's mission.

More than seven collaborative ef-

forts have been established in areas ranging from the identification of novel molecules responsible for pain initiation to measurement of pain in postoperative patients and the implementation of “comfort menus” aimed at individualizing patient pain management.

As one example, **Michael Caterina**, the institute's director, has worked with investigators from the departments of Neuroscience and of Anesthesiology and Critical Care Medicine to demonstrate that keratinocytes, the cells that cover our skin surface, can act as a “first line of defense” for the body by communicating with nearby sensory neurons and triggering the sensation of pain. This discovery provides the rationale for the development of novel pain

therapies aimed at interfering with the communication between keratinocytes and nerves to disrupt pain signaling.

In another collaboration, **Allan Belzberg**, the institute's clinical co-director, has worked with scientists in the Department of Neurology to uncover why some patients with peripheral nerve tumors experience excruciating pain, whereas others do not. By isolating the tumor cells from these patients, the team has discovered a number of pain-related genes that are expressed at higher levels in tumors from patients with pain compared with those whose tumors are not painful. Further analysis of these genes will provide an invaluable handle with which to better understand and ultimately treat pain in these patients. ●

# The Battle to Protect and Preserve Peripheral Nerves

**N**euromuscular disease expert **Ahmet Hoke** is charged with energy, just like the nerve fibers he is trying to reconnect in accident victims and wounded war veterans. For decades, researchers have searched for ways to stimulate injured ends of peripheral nerves to regrow and wend their way to endpoints in muscle and skin. Hoke's work in cell biology, stem cell research, nanotechnology and drug development is at the vanguard.

Injured nerves regenerate slowly—about 1 millimeter each day—and typically lose their bearing over time. Hoke and his colleagues want to accelerate the pace of regeneration and keep the nerve fibers on course. “As a clinician, I feel an urgency to improve patient care,” he says.

Working with the U.S. Department of Defense, Hoke and his bioengineering colleagues are developing nanotube technologies in which they fill tiny conduits with even tinier, spaghetti-like nanofibers and surgically implant them at injury sites to guide wayward nerve fibers. In a concept similar to fertilizing a flower garden, the researchers supply the nanotubes with nutritional nerve growth factors and Schwann cells, which naturally guide nerve fibers.

Hoke is lighting up other areas in the neuromuscular field, too, with his research to find ways to eliminate peripheral neurotoxicity, a common side effect of chemotherapy. Because it causes patients to develop unpleasant and sometimes debilitating numbness and weakness in their limbs, peripheral neurotoxicity is a major dose-limiting side effect of many chemotherapeutic drugs. It affects up to 80 percent of patients who get chemotherapy.

Several years ago, Hoke set out to screen thousands of chemical compounds as possible neuroprotective agents.

“We spent about five years and finally found an antioxidant called ethoxyquin that prevented nerve damage in cells in the laboratory,” he says. He and translational medicine experts at Johns Hopkins are now developing an ethoxyquin therapeutic compound for testing in clinical trials in humans.

Noting it has the potential “to prevent nerve damage in millions of cancer patients every year,” Hoke says. “I envision it being used like drugs we currently give chemotherapy patients to prevent nausea.” ●



○ **Challenge:** To repair damaged peripheral nerves and prevent peripheral neurotoxicity in patients treated with cancer drugs.

○ **Approach:** Hoke is developing nanotube technology to guide regenerating nerves and a therapeutic compound to prevent chemotherapy-related nerve damage.

○ **Progress:** Unique nanotube technologies are being developed to guide injured peripheral nerves. An antioxidant for preventing nerve damage caused by chemotherapeutic drugs is nearing testing in humans.

○ **Challenge:** To better understand chronic pain in order to develop new and effective treatment strategies.

○ **Approach:** Bringing together scientists from disparate fields across Johns Hopkins to collaborate on novel solutions that will fundamentally transform our understanding of pain and how to treat it.

○ **Progress:** In one collaboration, scientists have identified keratinocytes, the cells that cover our skin surface, as a target for novel pain therapies to disrupt pain signaling. In another, researchers have found genetic clues as to why some patients with peripheral nerve tumors experience excruciating pain, opening the door for better treatments.

🎥 **Watch Allan Belzberg and Michael Caterina explain current neurosurgical pain research projects at [hopkinsmedicine.org/doorways/pain](http://hopkinsmedicine.org/doorways/pain).**

# New Hope for Patients with SMA

**I**n a day and age when so many people are walking, running and in other ways exerting themselves for the sake of fitness, people with spinal muscular atrophy, or SMA, live in sharp contrast in their hope to simply stand or even sit upright.

SMA adversely affects the nerve cells (motor neurons) of the spinal cord that we need to maintain and control muscles for posture and physical activity. The most common genetic cause of death in infancy, SMA is classified into three types based on severity. While patients with less severe forms can live with it for years, babies born with the most severe form, type 1, usually die before their second birthday.

Fortunately, says neuromuscular disease specialist **Charlotte Sumner**, there is hope on the horizon. “We are closer to a treatment for SMA than for perhaps any other inherited neuromuscular disorder.”

Sumner is investigating how a mutation in the survival motor neuron 1 (SMN1) gene causes SMA, possible therapies for preventing SMA’s harsh consequences and the optimal timing for starting treatment. Mouse studies show that timing could be critical. “The motor neurons in SMA go down a path to cell death. We want to catch them while they are still capable of functioning,” she says.

The strategies that Sumner and her colleagues in the field are pursuing include examining compounds that will increase the presence of a protective protein produced by a related and omnipresent gene called SMN2. Research shows that having more SMN2 can override some, if not all, of the effect of a defective SMN1 gene. Sumner and her lab colleagues did one of the first studies showing that a drug that increases SMN expression could improve the motor ability of mice.

“The big challenge is to achieve a similar effect in humans,” says Sumner. They are working with pharmaceutical companies to develop and test several of the most promising compounds. One, an anti-

sense oligonucleotide (ASO), is in an early-phase trial to assess the safety, tolerability and optimal drug levels of the compound in infants with type 1 SMA.

“Patients with SMA and their families are deeply committed to fully living life and learning all they can about the progress we’re making,” says Sumner, who recently participated in an annual meeting of patients, families, researchers and clinicians. “A mother was telling me how much her son loves wheelchair ice hockey. I have never been more optimistic that before long—hopefully in less than five years—we will be offering children like him an early treatment that keeps motor neurons alive and muscles growing, and that paves the way to an active and long life.” ●

○ **Challenge:** To find a treatment for the genetic disorder spinal muscular atrophy, or SMA.

○ **Approach:** Sumner wants to increase the production of a protective protein.

○ **Progress:** Clinical trials are underway for testing the effect in humans of an ASO compound that kept motor neurons alive in mice with SMA.





Crawford, right, with patient Payton Mueller and Payton's mom, Rachele Krebsbach

## Strength Under Pressure

**T**om Crawford, a specialist in childhood motor neurons, has a long history of caring for children with SMA. He has treated more than 325 patients in his 30 years in the field. He also participated in the discovery of the SMA gene, testing new treatments and developing care guidelines.

Currently, he's working to standardize an approach to test the impact of experimental therapies for SMA—and he's making it entertaining.

"SMA is just one part of life," he says. "Children with SMA are bright, alert and attentive kids. I want to

make sure they don't forget to live well. To me, that's job number one." When his patients come to participate in clinical trials, "they laugh, learn and accomplish."

Crawford engages his patients who are old enough in what he calls a "rather quaint" approach to testing muscle strength. It involves a strength gauge that's specially designed to appeal to the kids' competitive and fun-loving spirit. "It has to be fun for kids to cooperate," he notes. Through use of the gauge, Crawford is collecting thousands of pieces of unique data

that shed light on the course of neuromuscular decline in SMA, to which treatment outcomes can be compared. "If we can understand decline, then we can understand what improvement looks like," he says.

"SMA has gone from the least hopeful to the most hopeful in the entire world of neurologic genetic disease," says Crawford. He adds, "I always wanted to make a difference. When I saw my first patient with SMA, I knew this was exactly the place for me." ●

# A Dietary Solution to Extreme Epilepsy

**E**ach year, about a dozen patients land in the Johns Hopkins neurosciences critical care unit with an often fatal condition called super-refractory status epilepticus (SRSE) related to conditions like stroke, traumatic brain injury, infection or tumors. The challenge for doctors is to quiet the extreme electrical storm in the brain, which can mean putting the patient into a medically induced coma.

The quiet has been hard to maintain, and about 40 percent of patients have traditionally died from SRSE. Until now, that is, thanks to an “Aha!” moment in which neurologist **Mackenzie Cervenka** and childhood epilepsy expert **Eric Kossoff** realized that they could potentially make an impact on SRSE based on what they know about dietary management of epilepsy in children.

“We thought it might be possible to control SRSE using an adult-sized version of a special ketogenic diet that works in kids,” says Cervenka. The diet mimics starvation by making the body burn fat, but it still provides necessary nutrients. It’s high in fat and low in carbohydrates and protein.

Using the ketogenic diet, the researchers have succeeded in bringing 90 percent of patients with SRSE out of the deep coma safely while stopping status epilepticus.

Cervenka and her Johns Hopkins colleagues—with others from Mayo Clinic, Rush University Medical Center, Oregon Health & Science University and The Queen’s Medical Center—recently launched a prospective multicenter trial in which a standardized ketogenic diet protocol will be used to provide further data about its ability to treat SRSE.

She is also applying a therapy called the modified Atkins diet to patients she regularly treats at The Johns Hopkins Hospital’s Adult Epilepsy Diet Center, which she also directs. Patients learn how to track their weight, urine ketones and number of seizures, and they receive recipes and information about the diet and the food they’ll be focusing on—including butter, eggs, bacon and mayonnaise—with formal training provided by a registered dietitian. “When I came to The Johns Hopkins Hospital in 2008 to work in epilepsy,” says Cervenka, “diet therapy for adults hadn’t even been part of my neurology training.”

Cervenka is even eating a version of the modified Atkins diet herself. “I’m doing it to share the experience with my patients and help them with food choices and diet ideas.” ●

○ **Challenge:** To increase survival of critical care patients experiencing super-refractory status epilepticus (SRSE) and improve seizure control in adult epilepsy clinic patients.

○ **Approach:** Cervenka implemented an adult-sized version of a special ketogenic diet that works in children.

○ **Progress:** A pilot study showed success in 90 percent of SRSE patients. A prospective multicenter trial is underway for standardizing the diet for use in treating SRSE.

Cervenka, left, with registered dietitian Bobbie Henry



# A Changing Ecosystem for Drug Discovery

The past decade has seen a landscape change in drug discovery, as the declining number of new drug approvals has forced many pharmaceutical companies to downsize their internal research and development operations and move toward partnerships with academia.

Enter the Johns Hopkins Brain Science Institute's (BSi's) NeuroTranslational Drug Discovery Program, led by **Barbara Slusher**. "The BSi's mission is to translate basic science discoveries into drugs that improve patient care," says Slusher, who joined Johns Hopkins in 2009 after 18 years of leading research and translational development in the drug industry.

In what she describes as "a changing ecosystem" in drug discovery, Slusher is building key partnerships with basic scientists at Johns Hopkins and the drug industry to find new drug treatments for neurological disorders—and speed their paths to market. In 2011, the BSi entered into a special collaborative, high throughput screening agreement with Tokyo-based pharmaceutical giant Eisai Co. Ltd. "With this, we put the program's mission on an accelerated course," says Slusher. Eisai is sharing its entire proprietary drug library

with the BSi for teasing out new treatments based on novel Johns Hopkins targets.

Slusher and her team are currently pursuing six drug discovery programs with Johns Hopkins faculty in a number of therapeutic areas, including schizophrenia, peripheral neuropathy, pain, neurodegeneration, multiple sclerosis and brain cancer. They have raised funds, signed licensing agreements with drug companies and spun out a new company, Cerecor Inc. They are demonstrating that innovation, depth of knowledge, research capabilities and understanding patient needs combine to make a highly productive environment for drug discovery.

Slusher is also working outside of Johns Hopkins to bring together this growing community around academic drug discovery. "Partnerships are the future of drug discovery in every field," she says. With colleagues from the University of North Carolina, Harvard, Vanderbilt and the University of California, San Francisco, she founded the Academic Drug Discovery Consortium (aD2c) to exchange know-how and create repositories of shared data and information. In less than two years, 110 academic centers and more than 1,000 individuals from around the world have become aD2c members. ●



## Parkinson's Disease Research

"New neuroprotective treatments for Parkinson's disease could be as few as three years away from clinical trials," says **Ted Dawson**, who studies the condition's molecular basis to better treat it.

His optimism stems from several recent discoveries. One is the role of the enzyme tyrosine kinase c-Abl in inactivating a protein called parkin, which causes toxic cellular debris to accumulate in dopamine cells, lead-

ing to dopamine cell death. (Parkinson's disease symptoms are caused by a selective loss of dopamine neurons in the substantia nigra of the brain.) In new work, Dawson found that c-Abl can itself be inhibited, which would leave parkin to carry out its normal job of degrading the cellular waste.

Crucially, c-Abl also causes a form of leukemia. "What is exciting here," says Dawson, "is that potent



○ **Challenge:** To translate Johns Hopkins discoveries into new drug treatments for neurological disorders.

○ **Approach:** Slusher and team are building drug discovery capabilities internal to Johns Hopkins; they also are educating and collaborating with faculty interested in drug discovery and translation.

○ **Progress:** Six Johns Hopkins drug discovery projects have been initiated, partnering agreements have been formed with pharmaceutical companies for three projects, a new drug discovery company was founded, new graduate courses in drug discovery courses have been initiated, and an international academic drug discovery consortium was founded and is flourishing.

## ers See Hope in Leukemia Drug

inhibitors have been developed to interfere with the c-Abl activity and successfully treat leukemia. Based on our data in a mouse model of Parkinson's, we believe that these c-Abl inhibitors should be able to slow the progression of Parkinson's, too." He is also looking for biomarkers in cerebrospinal fluid that could be used to evaluate the impact of these inhibitors on Parkinson's.

Dawson and colleagues are trying to determine which of the c-Abl-inhibiting drugs that are approved by the FDA for leukemia treatment have the best chance of success in Parkinson's. The researchers found that some c-Abl inhibitors are better at protecting dopamine neurons and restoring behavior deficits in mice than others—"probably due to better brain permeability," says Dawson. ●

○ **Challenge:** To slow progression of Parkinson's disease.

○ **Approach:** Dawson is performing testing in mice of an enzyme inhibitor approved for leukemia.

○ **Progress:** Dawson and team are comparing the effectiveness of a variety of brain-permeable c-Abl inhibitors and expect to be testing treatments in patients with Parkinson's soon.

# contact us

The Johns Hopkins departments of Neurology and Neurosurgery are here to collaborate with you at our locations throughout Maryland.

For more information about our services, [visit \*\*hopkinsmedicine.org/neuro\*\*](https://hopkinsmedicine.org/neuro) or call us at:

Adult Neurology 410-955-9441

Adult Neurosurgery 410-955-6406

Pediatric Neurology 410-955-4259

Pediatric Neurosurgery 410-955-7337

## Locations

### **The Johns Hopkins Hospital**

1800 Orleans St.  
Baltimore, MD 21287

### **Johns Hopkins Bayview Medical Center**

4940 Eastern Ave.  
301 Building, 3rd floor  
Baltimore, MD 21224

### **Johns Hopkins Health Care & Surgery Center**

10755 Falls Road  
Lutherville, MD 21093

### **Johns Hopkins Neurosurgery**

4927 Auburn Ave.  
Bethesda, MD 20814  
Direct: 301-896-6069

### **Howard County General Hospital Medical Pavilion**

10710 Charter Drive  
Columbia, MD 21044  
(Pediatric Neurosurgery  
and Sleep Medicine)

### **Anne Arundel Medical Center Clatanoff Pavilion**

2001 Medical Parkway  
Annapolis, MD 21401  
(Pediatric Headache)

## Referral Assistance

### **Hopkins Access Line (HAL)**

For urgent physician-to-physician referrals or consultations, call HAL at **1-800-765-5447**.

### **Johns Hopkins USA**

Johns Hopkins USA is a free medical concierge service designed to help patients traveling from outside of Maryland. Our staff can help identify appropriate physicians, coordinate multiple medical appointments, arrange second opinions and provide information about Johns Hopkins' services.

Call Johns Hopkins USA at **1-855-695-4872** (**1-855-MY-JHUSA**) or visit **[hopkinsmedicine.org/usa](https://hopkinsmedicine.org/usa)**.

### **Johns Hopkins Medicine International**

Our dedicated team—made up of more than 100 care experts from 30 countries—will serve as your guide to Johns Hopkins' world-class medicine. We seamlessly combine your medical needs, individual preferences, and cultural, linguistic and religious expectations into a tailored experience that makes Johns Hopkins feel as close to home as possible.

For inquiries outside of the U.S., call **+1-410-502-7683** or visit **[hopkinsmedicine.org/international](https://hopkinsmedicine.org/international)**.

### **Johns Hopkins Clinical Connection**

Hear from and connect with Johns Hopkins health care professionals sharing insights on the latest clinical innovations and advances in patient care. Register for your free membership to access videos, articles, news, clinical trials and much more at: **[hopkinsmedicine.org/clinicalconnection](https://hopkinsmedicine.org/clinicalconnection)**.

### **Physician Education**

Johns Hopkins Continuing Medical Education:  
**[hopkinscme.edu](https://hopkinscme.edu)**

