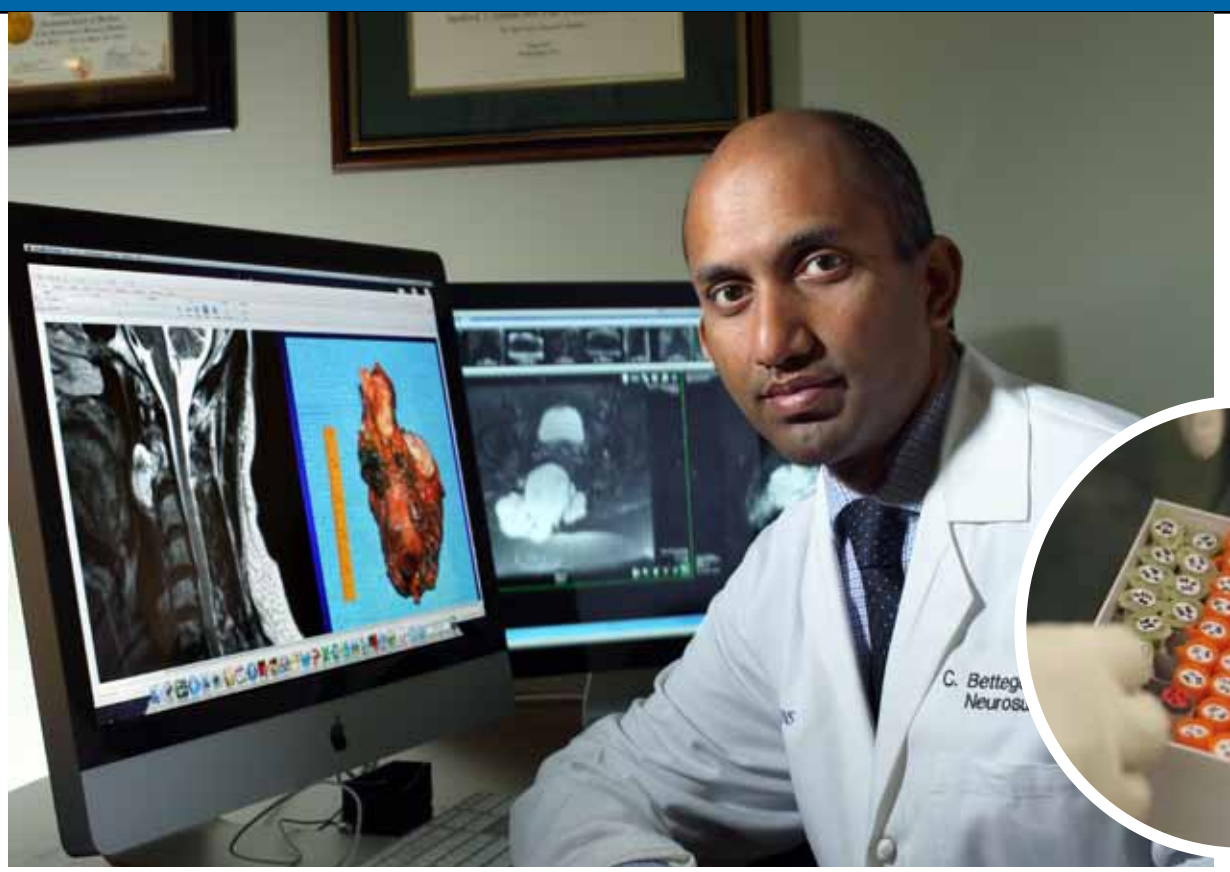
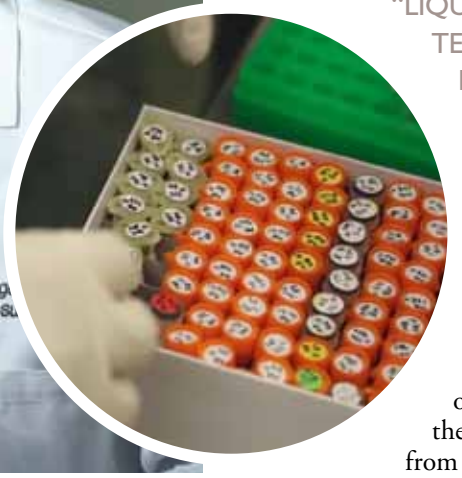
JOHNS HOPKINS
NeuroLogic

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

FALL 2015

JOHNS HOPKINS MEDICINE





BETTEGOWDA AND HIS COLLEAGUES ARE DEVELOPING WHAT THEY CALL "LIQUID BIOPSIES"—BLOOD TESTS THAT SHED SOME INFORMATION ABOUT TUMOR STATUS.

Liquid Biopsies for **Chordomas**

Chordomas, though rare, represent one of the most difficult cancers to treat and track. These tumors, thought to arise from remnants of the notochord, affect only a few hundred people in the United States each year. Surgery is the only treatment modality shown to significantly alter survival in large studies, but it comes fraught with its own challenges. Because many of these cancers recur locally—and are typically removed with en bloc resection with extensive spinal stabilization and plastic surgery reconstruction—subsequent surgeries are often more and more difficult, if not impossible.

To get around these problems, researchers are investigating new adjunct and targeted therapies, including various radiation methods, novel chemotherapies and immunotherapies. However, being able to determine whether these therapies are having their intended effect can be tricky—on MRI and CT scans, tumors might not change in size over time, or might look more or less dense, fibrotic, or necrotic.

"It's unclear whether these changes represent true changes in disease or are just an evolution of the tumor over time," says Johns Hopkins neurosurgeon **Chetan Bettegowda**.

To help track whether adjunct treatments are having their intended effect, doctors need tools beyond MRI and CT. That's why Bettegowda and his colleagues are developing what they call "liquid biopsies"—blood tests that shed some information about tumor status.

Chordomas are good candidates for this type of blood test, Bettegowda explains, because unlike many central nervous system tumors, early data suggest that they shed DNA into the bloodstream. By looking for particular biomarkers in this DNA that are unique to these cancers and tracking changes over time, researchers can more effectively assess chordoma growth and changes in response to adjuvant therapies.

Bettegowda and his colleagues are currently performing genetic testing on numerous samples gathered from chordoma patients at Johns Hopkins, searching for the minute differences that separate chordoma DNA from that of healthy cells. Concurrently, they're taking blood samples from patients before, during and after treatment to gauge how levels of chordoma DNA might rise or fall over the course of a therapy, a surrogate for how the tumor itself might be growing or shrinking. This type of test might also be used in the weeks and months immediately after surgery to look for minimally residual disease, Bettegowda says, and leftover cells that could lead to recurrence, and might suggest a need for more aggressive adjunct therapies.

The researchers are also pursuing a test for the rs2305089 single nucleotide polymorphism (SNP) located in the brachyury gene, a developmental gene known to play a role in notochord development. Bettegowda and his colleagues have shown that while the vast majority of individuals that develop chordomas have this particular SNP variation, those that develop chordomas without this SNP tend to have worse outcomes.

Developing a blood test for this SNP or chordoma DNA in general could lead to better clinical decision making for these challenging tumors, Bettegowda says. "Our ultimate goal," says Bettegowda, "is to be more selective in the therapies we deliver to treat these patients in the most effective way possible." ■

To refer a patient, call 410-955-6406.
International inquiries: +1-410-502-7683

To see a video in which Chetan Bettegowda discusses liquid biopsies to track cancer, please visit **bit.ly/liquid_biopsies**.

CEREBROSPINAL FLUID DISORDERS

Abhay Moghekar, left, and Mark Luciano of the Cerebral Fluid Center at Johns Hopkins, where neurosurgeons, neurologists, pain experts and therapists treat patients together.

Holistic Treatment for **CSF Disorders**

Hydrocephalus and cerebrospinal fluid (CSF) leaks stem from very different anatomical causes. But both fall under the umbrella of CSF disorders, conditions that change CSF pressure and lead to numerous related consequences, including a host of neurological symptoms. Though such disorders—which also include pediatric and adult hydrocephalus, Chiari malformations, pseudotumor cerebri, cerebral and spinal cord cysts, and periventricular tumors—are often treated in a fragmented fashion by different types of providers, concentrating expertise within a single group significantly benefits patients, says neurosurgeon **Mark Luciano**, who joined Johns Hopkins' Department of Neurosurgery in August.

"These conditions as a group are difficult to treat effectively," he says. "Patients often lack specialists in CSF disorders with the necessary knowledge to fully address their condition."

That's why Luciano and neurology colleague **Abhay Moghekar** co-director of the Cerebral Fluid Center at Johns Hopkins, where other neurosurgeons, neurologists, pain experts and therapists treat patients together.

> "THESE CONDITIONS AS A GROUP ARE DIFFICULT TO TREAT EFFECTIVELY."
>
> — MARK LUCIANO

One of the most common disorders seen through the program is adult hydrocephalus, explains Moghekar. Though hydrocephalus is often thought of as a pediatric disorder, it's typically treated with shunts, which require lifelong care. Patients who age out of pediatric care can have difficulty finding a specialist willing to follow up with them in adulthood. "We can help patients make a comfortable transition from pediatric to adult care," Moghekar says.

Adults also suffer from a unique type of hydrocephalus known as normal pressure hydrocephalus (NPH). This problem can be difficult to diagnose because its constellation of symptoms, including gait disturbance, urinary incontinence and cognitive problems, are common to many other diseases. NPH in particular requires the type of comprehensive, multidisciplinary care available only through a model like the Cerebral Fluid Center.

When patients come in for an NPH evaluation, Moghekar explains, a physical therapist tests their gait and balance, and a neurologist provides a comprehensive neurologic workup to assess for all potential diagnoses. If NPH is suspected, a spinal tap is performed with quantitative testing of gait and balance to determine if the patient would benefit from a shunt. If the patient's gait improves after the spinal tap, then it's a positive sign that a shunt might provide long-lasting relief, and the patient is referred to Luciano for shunt surgery.

Other conditions under the CSF disorders banner require their own unique amalgamation of expertise, Luciano adds, including geriatrics, ophthalmology, pain medicine and other specialties. "We truly provide a comprehensive combination of medical and surgical services to treat patients as effectively as possible." ■

To refer a patient to the Cerebral Fluid Center, call 410-955-7482. International inquiries: +1-410-502-7683

EPILEPSY

Halting Seizures with D-Leucine

The role of the amino acid D-leucine has been a mystery. Now, recent studies in mice, led by Johns Hopkins researchers and published in *Neurobiology of Disease*, suggest that it could play a vital role in halting seizures, offering a novel signaling pathway that differs from any of those currently targeted by anti-seizure medications.

"Epilepsy treatments over the last 50 years have not improved much, so there's an acute need for better therapeutic approaches, especially for the millions of people with drug-resistant epilepsy," says Johns Hopkins pediatric neurologist **Adam Hartman**. "If confirmed in larger animals and humans, our results carry a real promise for those suffering from unremitting seizures."

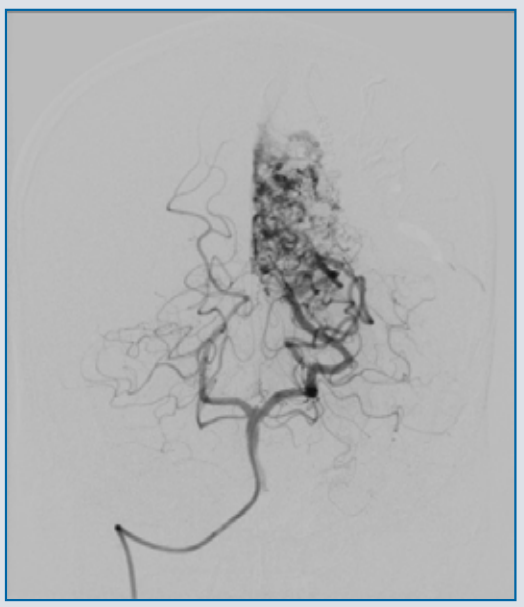
Hartman and his colleagues started out with the premise that certain amino acids may play a role in seizure prevention because they produce some of the same metabolic byproducts as high-fat ketogenic diets, an alternative therapy for patients whose seizures are not well-controlled on medication. A form of the diet was used as standard epilepsy treatment in the 1920s and 1930s during the pre-medication era but fell out of favor when the first epilepsy drugs emerged. An improved version of the diet, brought back into vogue by the late Johns Hopkins neurologist John Freeman and recently retired Johns Hopkins epileptologist Patti Vining, offered relief to countless children with drug-resistant seizures. However, the food regimen requires complex calculations, can be challenging to follow and doesn't always provide complete seizure control.

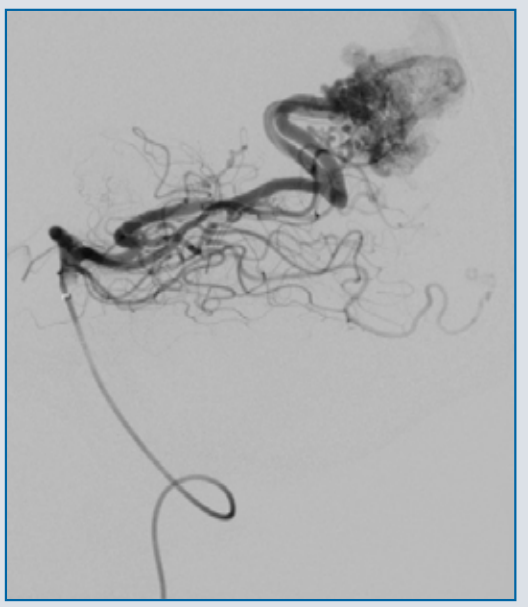
In an initial set of experiments, researchers pretreated mice with the amino acid L-leucine and another one, called D-leucine, which

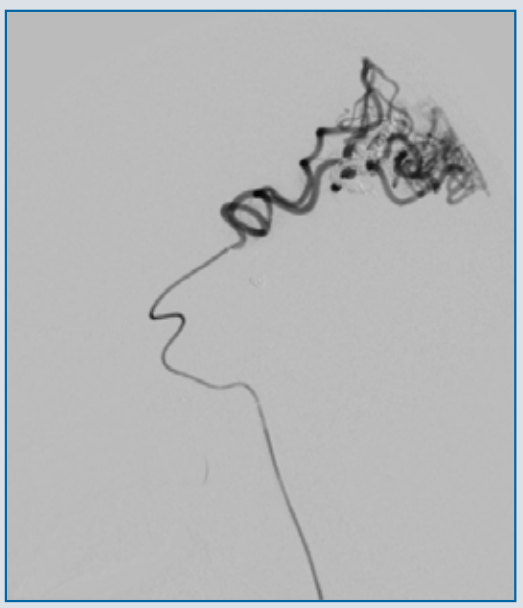
(continued on back page)

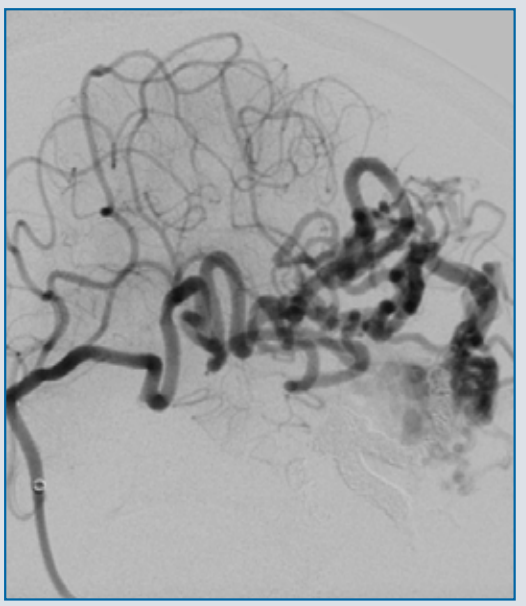
> "IF CONFIRMED IN LARGER ANIMALS AND HUMANS, OUR RESULTS CARRY A REAL PROMISE FOR THOSE SUFFERING FROM UNREMITTING SEIZURES."
>
> — ADAM HARTMAN

A New Way to Treat **Ischemic Stroke**









Victor Urrutia, Geoffrey Colby and Alexander Coon are using stentrievers to mechanically remove stuborn blood clots in the brain. The medical images show the effects of the treatment in action.

When the use of tissue plasminogen activator (tPA) was approved by the U.S. Food and Drug Administration in 1996, it was a watershed moment for stroke treatment. Many ischemic stroke patients who were destined for a lifetime of extreme disability or death often went on to live productive lives. However, notes neurologist and director of The Johns Hopkins Hospital's Stroke Center **Victor Urrutia**, tPA was an imperfect fix. When clots were lodged within the brain's larger arteries, or when significant time had passed, tPA isn't as effective.

However, new tools approved for use just three years ago could make the difference for patients when tPA doesn't. These devices, known as stentrievers, mechanically remove blood clots from the brain, providing a way to reopen arteries even when stubborn clots don't respond fully to tPA. Recent studies published in *The New England Journal of Medicine* showed that combining the use of stentrievers with tPA can increase the number of people living independently three months after stroke from 30 percent to nearly 70 percent.

THE NEW DEVICES ARE BASICALLY "STENTS ON A STICK" THAT OPEN WITHIN A CLOT.

"These are dramatic numbers of people helped with this new technology," says Johns Hopkins endovascular neurosurgeon **Alexander Coon**, who uses stentrievers in combination with tPA routinely in his practice.

The new devices are basically "stents on a stick" that open within a clot, explains Johns Hopkins neurosurgeon **Geoffrey Colby**. By threading the collapsed chicken-wirelike stent into a clot with a wire, then opening it, these devices interdigitate the clot's gelatinous material, allowing surgeons to easily grab it and remove even large clots buried deep within the brain. Blood flow is instantly restored, leading to less ischemic damage and, thus, better function for patients over time.

"Now, any patient who receives tPA could potentially be a candidate for these other therapies if they have a large order occlusion and don't show signs of an already concluded stroke in imaging," Colby says.

Because of the specialized nature of this therapy, Urrutia adds, it's mostly offered at certified Comprehensive Stroke Centers, such as The Johns Hopkins Hospital. These centers, numbering around 80 in the country, have the necessary concentration of experts and tools to effectively and safely deliver this therapy. For this reason, Urrutia says, he and colleagues across the nation are leading efforts to modify routing protocols for ambulances to deliver suspected stroke patients to Comprehensive Stroke Centers, even if they have to bypass other hospitals.

With the very clear and enormous success combining these stentrievers with tPA, it's clear that this treatment protocol is here to stay and has the promise of helping untold numbers of patients who wouldn't benefit from tPA alone.

"Just as tPA changed the way we take care of stroke in 1996," Urrutia says, "endovascular therapy is leading to an exciting new era." ■

To refer a patient, call 410-955-6406.
International inquiries: +1-410-502-7683

Halting Seizures with D-Leucine

(continued from page 2)

has an identical structure to L-leucine except it is its biochemical mirror image. When researchers induced seizures with an electric shock, animals pretreated with either amino acid fared better, developing seizures at notably higher electric currents than mice that received placebo, a sign of greater seizure resistance.

To see whether D-leucine and L-leucine could also interrupt ongoing seizures, researchers induced seizures in a group of animals and, once convulsions began, they administered low and high doses of both amino acids. L-leucine failed to abort ongoing seizures, while D-leucine effectively interrupted convulsions. Strikingly, the researchers say, D-leucine terminated seizures even at low doses.

Next, researchers compared the ability of D-leucine to terminate prolonged, unrelenting seizures against the sedative diazepam, commonly used to stop such seizures in humans. Both treatments terminated seizures. In addition, mice treated with D-leucine resumed normal behavior faster and experienced none of the drowsiness and sluggishness observed in animals treated with the drug, also common side effects seen in human patients.

A final set of experiments showed that D-leucine interacted with none of the signaling pathways known to spark or avert seizures.

"Our results suggest that D-leucine affects neurons differently from other known therapies to control seizures," says Hartman's colleague **J. Marie Hardwick**, a microbiologist and immunologist at the Johns Hopkins Bloomberg School of Public Health. "This finding gives us hope of new approaches to epilepsy on the horizon. ■

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

NeuroLogic

Johns Hopkins Medicine
901 S. Bond St., Suite 550
Baltimore, Maryland 21231

This newsletter is published for the Departments of Neurology and Neurosurgery by Johns Hopkins Medicine Marketing and Communications

Departments of Neurology and Neurosurgery
Justin McArthur, M.B.B.S., M.P.H., *Director of Neurology*
Henry Brem, M.D., *Harvey Cushing Professor and Director of Neurosurgery*

Marketing and Communications
Dalal Haldeman, Ph.D., M.B.A., *Senior Vice President*
Justin Kovalsky, *Managing Editor*
Christen Brownlee, *Writer*
Lori Kirkpatrick, *Design*
Keith Weller, *Photography*

Info: hopkinsmedicine.org/neuro

Non-Profit Org
U.S. Postage
PAID
Permit No. 5415
Baltimore, MD

NeuroLogic

FALL 2015

JOHNS HOPKINS MEDICINE

NEWS FROM THE JOHNS HOPKINS DEPARTMENTS OF NEUROLOGY AND NEUROSURGERY

Inside