JOHNS HOPKINS
NeuroLogic

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

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JOHNS HOPKINS MEDICINE

Innovations in Care for Patients with Pediatric Epilepsy

For difficult epilepsy cases, Johns Hopkins experts use the latest, less invasive diagnostic and treatment tools.

Sarah Kelley, director of the pediatric epilepsy monitoring unit, watches as a patient and child life specialist Crissie Traugott play music together while the patient's brain activity is monitored.

Within the Johns Hopkins departments of neurology and neurosurgery, recent advancements in pediatric epilepsy care have resulted in vastly more precise and less invasive ways to diagnose, monitor and treat the source of seizures for patients with the condition. The department's faculty members and clinicians are adept at caring for those with intractable epilepsy and for whom multiple medicines have failed.

"Our specialty is evaluating patients with difficult-to-control epilepsy," says **Sarah Kelley**, director of the pediatric epilepsy monitoring unit, which opened in January 2020 and allows for quick admission and evaluation in a child-friendly environment. "We're able to quickly bring patients in and give them the services they need."

Along with high-resolution MRI, the care team uses stereoelectroencephalography (SEEG) technology, which involves placing tiny electrodes in the brain to pinpoint specific areas that cause seizures, allowing physicians 3D spatial and temporal imaging.

"Instead of having a large window of the skull removed, we make tiny holes in the skull using software and a robot," says pediatric neurosurgeon **Dody Robinson**, who is a nationally recognized expert in the treatment of pediatric epilepsy and spasticity. "It adds a lot more precise information, and can help us potentially remove the area that's causing the seizures."

"WE HAVE EXTENSIVE RESOURCES IN TERMS OF HELPING THE WHOLE PERSON. IT'S VERY REWARDING TO BE ABLE TO HELP THESE KIDS GET THEIR LIVES BACK."

— DODY ROBINSON

Laser ablation is also a treatment option for particular patients. The technique can be particularly effective for those with focal epilepsy. Rather than removing part of the brain with open surgery, Johns Hopkins neurosurgeons use laser ablation's high-tech planning software and advanced imaging to create a tightly controlled, localized lesion. The care team has seen great efficacy in highly selected patients, Robinson says, and the approach reduces potential postoperative pain and cognitive issues, as well as the time children spend in recovery from several days for a typical open surgery to 24 to 48 hours.

The group is also treating certain pediatric patients with vagus nerve stimulators (VNS) and responsive neurostimulation (RNS).

In addition to intractable epilepsy and drug-resistant epilepsy, the departments' clinicians specialize in treating patients who have already had surgery and continue to have seizures as well as patients looking for dietary therapy and other interventions.

Because of the collaborative and multidisciplinary nature of the work, pediatric patients have access to a breadth of opportunities for care. "We're able to treat the patient holistically with our colleagues in neuropsychology and other specialties to really help these kids get as close to typical as possible," Robinson says. "We have extensive resources in terms of helping the whole person. It's very rewarding to be able to help these kids get their lives back." ■

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A gene therapy clinical trial may open up new possibilities for the treatment of Duchenne muscular dystrophy.

Pictured: A conceptual illustration of a DNA helix.

Gene Therapy for Duchenne Muscular Dystrophy

A new clinical trial set to begin in early 2021 at Johns Hopkins will test innovative way of treating the devastating genetic disorder.

Though long-established treatments for Duchenne muscular dystrophy (DMD), such as corticosteroids, and newer treatments, such as exon-skipping therapies, can extend the time it takes for the disease's grim symptoms to take hold, no available therapy can halt the condition's progression, or — more optimistically — reverse it, explains Johns Hopkins neurologist **Jessica Nance**.

However, a clinical trial taking place soon at Johns Hopkins may have potential to bring this lofty goal to fruition, by using gene therapy to help repair the source of disease.

Nance explains that DMD is caused by deletions, duplications, point mutations or premature stop codons in the gene that makes dystrophin, a protein that stabilizes muscle cell membranes and supports the contractile apparatus. Without this protein, damage builds up over time, leading to muscle scarring, inflammation and eventually atrophy. Boys with this X-linked condition often progress on a neurotypical track for the first few years of their lives. But around the age of 4, Nance says, the lack of dystrophin begins to cause noticeable symptoms, causing gains in motor milestones to recede.

Prompting muscle cells to produce this missing protein would effectively cure the condition. Unfortunately, the gene that encodes dystrophin is large, making it difficult to fit inside current gene therapy vectors. However, says Nance, the new trial uses a workaround that partially fixes this problem: The dystrophin gene is trimmed down into "micro-dystrophin," leaving only the essential pieces.

In June 2020, researchers at Nationwide Children's Hospital in Columbus, Ohio, reported promising results from a phase 1/2 trial of this same gene therapy in a group of four young DMD patients, none of whom had yet started on corticosteroid therapy. After administering a single intravenous dose, this open-label trial followed participants for a year to assess safety, micro-dystrophin expression in muscle biopsies and functional outcomes in motor skills.

Not only was this therapy well tolerated, says Nance, but biopsy results showed that participants were producing micro-dystrophin and had begun doing the unimaginable — regaining lost motor function.

She hopes to see the same, she says, when she and her colleagues begin the next phase of the trial at Johns Hopkins in early 2021. They plan to recruit up to five boys under the age of 8. Although this trial will be randomized at first, study subjects on the placebo will eventually receive gene therapy if results continue to show potential.

"DMD has always been a terrible diagnosis to deliver," she says. "But these conversations are starting to change because of the hope that new therapies may provide. This trial moving forward could be a big step toward getting meaningful treatment for these kids." ■

"DUCHENNE MUSCULAR DYSTROPHY HAS ALWAYS BEEN A TERRIBLE DIAGNOSIS TO DELIVER, BUT THESE CONVERSATIONS ARE STARTING TO CHANGE BECAUSE OF THE HOPE THAT NEW THERAPIES MAY PROVIDE."

— JESSICA NANCE

☎ TO DISCUSS THE CLINICAL TRIAL OR REFER A PATIENT, PLEASE **CALL 410-955-4259**.

Individualized Care Through Translocation Testing

Johns Hopkins is among the few centers in the U.S. that identify tumors' unique features using on-site fusion tests.

Knowledge is power — particularly for cancers in the age of personalized medicine, says Johns Hopkins neurosurgeon **Chetan Bettegowda**. In the past, he explains, a patient's care team made decisions with a limited amount of information. However, a growing number of tools are providing a deeper look inside tumor cells' inner workings, giving insight that can shed light on prognosis and help doctors precisely target treatments. The latest members of this armamentarium, he says, are translocation tests that can be performed at Johns Hopkins.

These tests, Bettegowda explains, identify rearrangements in genetic material that occur when a piece of one chromosome breaks off and fuses with another chromosome. Translocations are hallmarks of many types of cancers treated by Johns Hopkins' neurosurgical service, including various types of gliomas, carcinomas and sarcomas. Identifying common translocations in these tumors can help providers understand the specific tumor subtype a patient has and might provide information on a patient's short- and long-term prognosis. More excitingly, Bettegowda says, for some tumor subtypes, translocation testing can identify rearrangements that can be targeted by newer medications.

"Historically, the only way we've been able to detect these translocations has been quite laborious, requiring a significant amount of time and effort to seek out potential rearrangements one by one. Patients often had to send samples, sometimes at significant personal expense, to outside companies for this service," Bettegowda explains. "New technology has revolutionized this task, allowing us to identify many translocations at once."

Patients can now access these tests through an order from their physicians at Johns Hopkins. Using a biopsy, the

Developing Implantable and Wearable Technology to Treat Spinal Cord Injury

Johns Hopkins neurosurgeons and biomedical engineers work to create wearable and implantable devices enabling continuous, postoperative treatment of acute, subacute and chronic spinal cord injury. The effort is funded by a $13.48 million grant from the Defense Advanced Research Projects Agency.

From the moment a patient arrives at The Johns Hopkins Hospital with a spinal cord injury that is treatable by surgery, clinicians prepare for spinal decompression and a procedure for stabilization. But after an operation is performed, "we can't monitor the spinal cord and provide treatment interventions in real time," says **Nicholas Theodore**, director of the Johns Hopkins Neurosurgical Spine Center. That all may change, however, thanks to a $13.48 million grant from the Defense Advanced Research Projects Agency and a team of Johns Hopkins neurosurgeons and biomedical engineers, working in tandem with academic and industry partners.

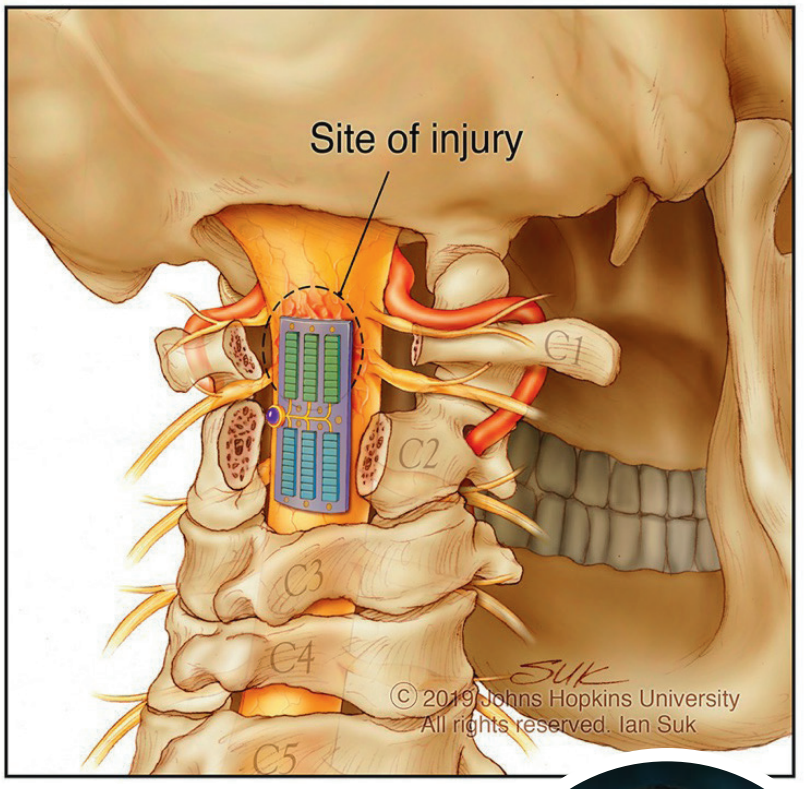
The group — led by Theodore and biomedical engineer **Amir Manbachi** — is developing both implantable and wearable devices to be implemented at the time of surgery to allow continuous, postoperative treatment of acute, subacute and chronic spinal cord injury. The technologies' shared purpose is to prevent secondary injury such as neurological damage, hypoxia, neurogenic shock, hemorrhage, edema and glial scarring, and to promote immunomodulation and neuromodulation for lower extremity muscle function, cardiovascular stability and bladder function.

The team's goal is to build and test three implantable devices and three wireless wearables that would work together to monitor perfusion pressure, oxygenation, intrathecal pressure, temperature and other biomarkers, as well as deliver interventions.

"If we could measure, monitor and treat the perfusion pressure of the spinal cord continuously over the course of a week or more after surgery, it would give us a real opportunity to improve outcomes," says Theodore.

The technology includes a multifunctional implant that would be placed epidurally at the site of the injury to perform ultrasound imaging, focused ultrasound, biomarker sensing and electrical spinal stimulation; an epidural electrical spinal stimulator; and an acute CSF management implant in the subarachnoid space that would monitor intrathecal pressure, oxygenation and temperature of CSF. Communication between the CSF management implant and the multifunctional implant would allow precise drainage of CSF and restoration of autoregulation.

The wireless wearables include a blood pressure imaging sensor, a bladder volume imaging and pressure sensor, and an electromyography and accelerometry tracking sensor. These technologies would deliver real-time data to one software application that will help inform treatment decisions.



The multifunctional implant shown here would be placed epidurally at the site of the injury to perform ultrasound imaging, focused ultrasound, biomarker sensing and electrical spinal stimulation.

Today, there is no way to consistently monitor opportunities for promising interventions such as CSF drainage and maintenance of mean arterial pressure, says Theodore. Likewise, he believes electrophysiological and ultrasound stimulation may hold promise for patients, and one of his first priorities is testing how pulsed ultrasound affects blood flow and exploring ways it can be used therapeutically as well as diagnostically.

The team aims to have an FDA-approved technology that could be used in clinical trials by the end of the five-year grant period.

"We have the top neurosurgery department in the country combined with the top biomedical engineering department in the country on this project," says Theodore. "I'm extremely optimistic about the possibilities." ■

"IF WE COULD MEASURE, MONITOR AND TREAT THE PERFUSION PRESSURE OF THE SPINAL CORD CONTINUOUSLY OVER THE COURSE OF A WEEK OR MORE AFTER SURGERY, IT WOULD GIVE US A REAL OPPORTUNITY TO IMPROVE OUTCOMES."

—NICHOLAS THEODORE

☎ TO LEARN MORE ABOUT THIS RESEARCH OR REFER A PATIENT, PLEASE **CALL 410-955-4424**.

pathology department at Johns Hopkins will run one of three distinct panels to identify different types of fusions. One is an actionable fusion set, designed to recognize various types of translocations that can be treated with targeted drugs. Another is a carcinoma fusion set, which identifies translocations common to these tumors that arise in epithelial cells. The third is a comprehensive panel that searches for all known types of translocations — knowledge particularly useful for sarcomas, connective tissue cancers that tend to have few mutations but frequent fusions.

Performing this testing within Johns Hopkins' own labs — a service offered by few medical centers in the U.S. — makes results immediately available to every member of the treatment team through patients' electronic medical record. Besides offering information that could be useful for current patients' prognosis and treatment, the knowledge gathered from translocation tests is helping guide research efforts that could help those facing these cancers in the future, a boon in a field that is advancing quickly, Bettegowda says. ■

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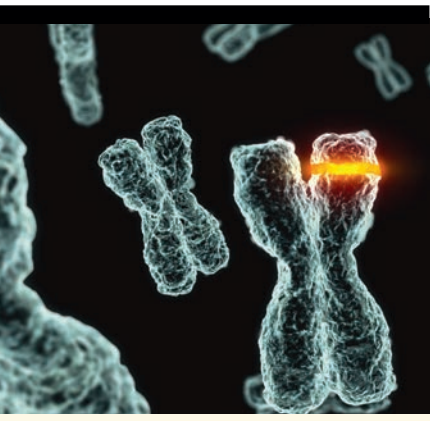
"WE'RE BECOMING BETTER AND BETTER AT IDENTIFYING THE MOLECULAR FEATURES THAT MAKE EACH TUMOR UNIQUE."

—CHETAN BETTEGOWDA



Johns Hopkins physicians now have rapid ways to identify changes in DNA, as depicted in amber on a chromosome, that could help guide treatments for patients with tumors of the central nervous system.

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Inside