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 provides a diverse and inclusive environment that fosters intellectual discovery, creates and transmits innovative knowledge, improves human health, and provides medical leadership to the world.

core values

Excellence & Discovery
Leadership & Integrity
Diversity & Inclusion
Respect & Collegiality
Faced as we in neurology and neurosurgery are with the daunting complexity of the nervous system and its often-devastating disorders, it’s all the more thrilling to be able to report significant advances in patient care and translational research. Here at Johns Hopkins, the progress has been happening on numerous fronts, and we wanted to share some of the promising innovations that we think could significantly improve patient outcomes and that in some cases are doing so today.

In enlisting implanted electrodes to determine optimal tissue-removal sites for relieving severe seizures, for example, Nathan Crone has been combining the data from many patients to build a general map of brain function that could prove invaluable to treating not only epilepsy but other disorders. John Laterra has been developing a monoclonal antibody for a brain-cell growth-factor receptor believed to promote glioblastomas, discovering more recently that the antibody might also help cut the tumors off from stem cells that lead to drug resistance.

Rafael Tamargo is saving patients with giant aneurysms by surgically rerouting blood flow around them via transplanted blood vessels, and he’s also investigating drugs that can counter post-brain-bleeding inflammation that sometimes leads to strokes. And Alex Coon is working with newly FDA-approved stents that are treating some of the largest aneurysms.

The challenges that yet remain are considerable. But the breadth and depth of the progress we’re seeing provide good reason to believe that disorders which not long ago seemed intractable may well be tamed within a generation. We hope you’ll share our excitement at the pushing forward of the boundaries of what we can do for patients.

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
The Hunt for a Brain-Tumor Vaccine

W ouldn’t it be great if we could cure brain tumors with a shot and make sure they never came back?” asks Michael Lim. There’s reason to be hopeful that this sort of extraordinary breakthrough is on the horizon, thanks to research being conducted by Lim, a neurosurgeon-scientist who directs the Johns Hopkins Metastatic Brain Tumor Center, and Johns Hopkins neuroscience researcher Betty Tyler and other colleagues.

Their research mainly targets glioblastomas, brain tumors known for their aggressive growth and the difficulty of treating them. Drugs can slow the tumors’ growth, and to help these drugs pack their toxic punch against the tumor and not elsewhere, neurosurgeon Henry Brem and Johns Hopkins researchers developed dissolving polymer wafers that can be implanted at the tumor site. Now Tyler is among those who have been conducting animal studies to determine which drugs work best with these wafers. Tyler, Brem and others are also looking at implantable microchips that can be programmed to release multiple drugs at different rates, times and sequences to avoid drug interactions. “There’s a constant push here to get just the right combination and timing of drugs to wipe out the tumor with minimal harm to the patient,” says Tyler.

Lim, meanwhile, is trying to find ways to get the body’s immune system to attack the tumors. “Our immune systems kill cancerous cells all the time,” he says. “But some cancer cells develop the ability to turn off the immune system response, and those are the ones that become tumors.” Lim and others are investigating molecules that seem to block the chemical signals that a tumor secretes to steer away immune cells. Lim’s lab is also working with antibodies that allow the immune cells to ignore the suppressive signals and come charging in to kill the tumor cells. In the laboratory, these antibodies have cured mice with glioblastomas, suggesting the antibodies may be a key step towards a brain-tumor vaccine. A clinical trial of the antibodies for glioblastoma patients will be starting soon. “We want to give patients immunity to these tumors in the truest sense of the word,” says Lim. “We still have a long way to go, but we’re very excited about the progress we’re making.”

● Challenge: Stop aggressive brain tumors
● Approach: Deliver drugs on microchips and energize the immune system
● Progress: Mice have been cured; patient trials are starting

Turning the Tables on Brain Tumors

T here’s a particular urgency to the quest to find a drug effective against the brain tumors called glioblastomas. Because they’re a form of cancer that spreads quickly through the brain, surgery and radiation usually can’t get at all the cancerous cells. “We need more creative ways of fighting this disease,” says Gregory Riggins, a cancer researcher in the neurosurgery department of Johns Hopkins. Riggins is unleashing more than his share of creativity in the battle, helping to come up with an unexpected and promising strategy for a drug that could wipe out glioblastoma cells while leaving normal brain cells unscathed.

The first important clues to the strategy came when Riggins and others collaborated about five years ago with renowned Johns Hopkins researcher Bert Vogelstein to try to identify which genes in a cell could be linked to glioblastomas. They discovered that mutations in a gene called IDH1 seemed to play a role in the tumor’s formation. But what did the gene do? A crucial insight came from another Riggins collaborator, cancer researcher Chi Dang. Dang suspected that IDH1 was producing an enzyme that was using up one of the key molecules needed for a cell’s metabolism, forcing the glioblastoma cell to rely on a different enzyme to get the energy it needed. Riggins and his collaborators saw that as a vulnerability they
might be able to exploit. “Cancer cells usually alter themselves to gain an advantage over other cells,” he explains. “Now we saw we might have a chance to turn the tables on them.”

If they could find a drug that interfered with the enzyme that only glioblastoma cells depend on for energy, then those cells would essentially starve, while normal cells continue to produce energy. Riggins and his collaborators soon found a compound that seemed to do the trick. Unfortunately, the compound doesn’t make for a good drug because of difficulties in getting it into the brain and into cells. So Riggins’ group is working furiously to tweak the compound to make it a better drug candidate, as well as to find more suitable compounds that can perform similarly.

“It’s all part of the long process of developing a new drug,” says Riggins. “But at least now we have an approach for selectively targeting glioblastoma cells, and that’s a huge first step.”

- **Challenge**: Starve brain-tumor cells without hurting other cells
- **Approach**: Block an enzyme that only glioblastomas rely on for energy
- **Progress**: Work is focusing on modifying a blocker to get it past the blood-brain barrier
A Rare Chance to Cure a Difficult Cancer

Ziya Gokaslan tells the graduate students who come to join his research at the Johns Hopkins Neurosurgical Spine Center that they have a shot at something that most researchers can only dream about: developing a full cure for a deadly form of cancer. “That’s not something we can say very often,” explains Gokaslan.

The target of Gokaslan’s efforts is chordoma, a malignant tumor that grows along the spine anywhere between the skull and the tailbone, gradually damaging nearby nerves and bone, causing pain, weakness and a loss of function. Gokaslan’s team is attacking these life-threatening tumors—diagnosed in about 300 people each year in the United States—on several fronts. Because the tumors surround and invade the spine, surgically removing one of these tumors whole is difficult. And if the tumor ruptures, it will recur. So Gokaslan and colleagues have helped develop a surgical technique that involves coming at the tumor from several different directions. “Each different angle gives us a better shot at safely freeing up one part of the tumor, so we can get it out in one piece,” says Gokaslan. “Then we can reconstruct part of the spine if it’s damaged, so the patient can regain mobility.”

Gokaslan and colleague Jean-Paul Wolinsky have also helped develop new surgical techniques for patients whose tumors are too entwined with bone and tissue to be removed whole, often the case with tumors at the base of the skull. Guided by advanced computer imaging, he can remove the tumor in pieces through a tube inserted in the neck, avoiding damage to the face and jaw that’s otherwise typical of the surgery. He’s also pioneering the use of radiation consisting of focused beams of protons to demolish the tumors, cutting treatment times down from two months to two days, and reducing the chances of recurrence.

What most excites Gokaslan, though, is the work his team and colleague Alfredo Quiñones-Hinojosa have done with the single, overactive gene believed to be mostly responsible for chordoma. That gene provides a unique opportunity, because most cancers are caused by activity in 200 or more genes, presenting too complex a target. Gokaslan and colleagues have helped identify compounds that, when injected into mice that have chordomas, seem to shut the gene down and stop tumor growth. “We’re still exploring different strategies,” says Gokaslan. “But having a way to silence this gene, combined with better surgery and radiation, means we have a real chance to cure chordoma.”

- Challenge: Remove chordomas cleanly and less invasively—and even curing them
- Approach: Guide surgery with computers, and shut down the gene that causes them
- Progress: Chordomas are coming out intact, and drugs have stopped tumor growth in mice
Letting the Hounds Loose on Brain Tumors

Alfredo Quiñones-Hinojosa has devoted his career to helping brain-tumor patients, in both the operating room and the laboratory. But the Johns Hopkins neurosurgeon prefers to emphasize what many of his patients do to help him—namely, grant him permission to keep and study any brain tissue he removes during surgery to get at a tumor. “It’s an enormous gift,” he says. “It makes everything I do possible.”

What Quiñones does with that gift is work to figure out how to get the brain to fight tumors on its own. To that end, he has helped uncover evidence that some of the cells in the brain may be stem cells. And the particular stem cells on which Quiñones focuses, a type found in fat tissue, have a unique property: They seek out brain tumors. “These are very smart cells,” he says. “Like a dog on the hunt, they follow a chemical signal to zero in on the tumors.”

Scientists aren’t sure what effect these stem cells have on tumors. But it doesn’t matter, says Quiñones, because he intends to alter the cells to aggressively attack them. “I want to give the cells weapons, and turn them into the Special Forces of the brain,” he says. He notes that a highly targeted antitumor therapy that comes from the patient’s own body might not be as hard on the patient as chemotherapy and other conventional therapies sometimes are—and could potentially be more effective.

The trick for Quiñones will be figuring out how to usefully alter the stem cells. Part of the problem is that everyone’s cells are different, and each person’s brain tumor is unique as well, which means the stem cells would have to be custom tailored in each case to fight a specific tumor. But Quiñones thinks he may have a strategy for doing exactly that. His idea is to take tumor and stem cells from a patient and determine by working with mice exactly the right way to turn those stem cells against the tumor.

“My dream is that every patient treated for a brain tumor will have that weapon waiting in case there’s a recurrence,” he says. “We can’t say this would be a cure, but it might make brain cancer a much more treatable and tolerable disease.”

Challenge: Use the patient’s own cells to effectively fight brain tumors

Approach: Modify stem cells from the patient’s brain to seek out and destroy tumor cells

Progress: Tumor-seeking stem cells have been found in the brain; making them deadly is under study
Red blood cells are life-giving—as long as they stay confined to the insides of blood vessels. When there’s internal bleeding, on the other hand, erythrocytes can be life-threatening, especially for patients with a ruptured aneurysm or other source of bleeding in the brain.

It’s a problem that has kept Johns Hopkins neurosurgeon Rafael Tamargo as busy in the lab as in the operating room. Tamargo is studying ways to prevent the narrowing of brain blood vessels that occurs in more than 50 percent of patients in the days after a brain hemorrhage. About half of those patients with vasospasms suffer a stroke. Most researchers thought the culprit was the muscles in the artery walls, but in fact, says Tamargo, “the problem is inflammation.”

When red blood cells spill into tissue, the hemoglobin they carry is immediately grabbed by the protein haptoglobin. The combined molecule signals immune system cells to attack the now-toxic erythrocytes and whisk their remnants away through lymphatic vessels, the inflammatory process that causes swelling and bruising. But because the brain has no lymphatic vessels, immune system cells that respond to cerebral hemorrhaging linger, die and break down, releasing molecules that cause the brain’s blood vessels to narrow. In some patients, that triggers vasospasm and stroke.

But why in some patients and not others? Tamargo was among those who suspected the culprit was a second, more inflammatory version of haptoglobin that only some people carry. Studies have shown that mice carrying this type-2 haptoglobin suffer strokes after brain bleeding, while those without it don’t. “At first,” says Tamargo, “people were skeptical when I and others said it was the haptoglobin. Now it’s a hot idea.”

Tamargo is working to identify drugs that can counter the inflammatory response and the narrowing of blood vessels following cerebral hemorrhage. He’s currently focusing on nitric oxide, a neurotransmitter that, among other things, dilates blood vessels. “If we can find a drug that stimulates the body to produce more nitric oxide,” he says, “it might prevent vasospams.”

And that would give patients who’ve had a cerebral hemorrhage one less thing to worry about.

| Challenge: | Post-bleeding spasms in brain blood vessels that can lead to strokes |
| Approach: | Counter inflammation from the protein that cleans up hemoglobin |
| Progress: | Compounds that counter inflammation are under study |

When a thin, weak segment of one of the blood vessels in the brain swells with blood and threatens to rupture, the aneurysm can be repaired by one of several techniques. But which technique is best? “There are risks and benefits to each approach,” says Alex Coon, one of a small number of neurosurgeons who can perform any of the procedures. “It’s important to consider each case on its own and make a very patient-centered decision.”

The two most common options are clipping and coiling. Clipping, developed 75 years ago at Johns Hopkins, involves placing miniature clamps on the neck of the aneurysm to seal it off. Coiling is a more recent alternative in which a metal coil is inserted through a small opening in an artery in the leg and threaded through other...
arteries until it’s finally pushed into place at the aneurysm. The coil causes the blood in the aneurysm to clot, again sealing it off. A metal stent is typically placed next to the coil to provide support and allow normal blood flow. One recent development called a pipeline embolization device combines the features of a stent and coil into one tube, simplifying placement.

Patients who undergo coiling can be back at work in two days, while clipping requires a week in the hospital and at least a month of recovery. But coiling, backed by less than 20 years of usage, is not yet known to be a permanent repair.

“We can’t say for sure that a 40-year-old with a coil won’t have to come back for another procedure,” says Coon. “Some patients say they don’t mind that risk, but for others it doesn’t make as much sense.”

Larger aneurysms aren’t good candidates for coiling, and Coon’s colleague Rafael Tamargo notes that even clipping can’t treat the very largest ones. Such “giant” aneurysms, says Tamargo, require redirecting the blood flow around the aneurysm with a section of blood vessel taken from the patient’s arm or leg. Johns Hopkins is one of a small number of medical centers that perform this complex surgery.

But Coon is confident that all aneurysm patients will have even more—and better—treatment options over time. “These are exciting times in the field,” he says.

- **Challenge:** Repair aneurysms before they rupture
- **Approach:** Emplace a coil in the aneurysm to seal it, and reroute blood vessels
- **Progress:** Coil patients are back at work in two days; even giant aneurysms are being repaired
Not long ago a couple brought their 3-month-old child to Johns Hopkins to see pediatric neurosurgeon Edward Ahn because the infant’s head wasn’t developing into a typical shape. The father thought he knew why—because he himself had been born with the same condition: craniosynostosis. Correcting it in the father had been an ordeal, but the infant in Ahn’s office would have a very different experience.

“We’ve been making huge changes in how we treat this condition here at Hopkins,” says Ahn.

The several bony plates that make up the skull are normally not yet attached to one another in a newborn, allowing the infant’s head to expand in all directions in the coming months to accommodate the rapidly growing brain. In babies with craniosynostosis plates fuse prematurely, constricting skull growth in one direction and forcing the skull to compensate by growing excessively in other directions.

The traditional treatment, typically performed when a child is between 6 months and a year old, is surgery to break up and reconstruct the plates. It’s a long operation requiring an ear-to-ear incision as well as transfusions to compensate for considerable blood loss. “It’s a week in hospital, and it may require additional surgeries to improve the results,” says Ahn. “Neurosurgeons really wanted to rethink the approach.”

Today Ahn needs to make only two tiny incisions on an infant’s head to accommodate the camera of an endoscope and a tiny cutting tool for removing a thin strip between the plates to free them. The procedure is so fast and neat that transfusions usually aren’t required, and the infant can go home the next day. And it can be performed on children as young as 2 months, an age at which all the plates are still shifting.

Following the operation, the child is fitted with a helmet that helps mold the head into a perfectly normal shape over the next nine or so months. “The babies don’t mind the helmet,” says Ahn. “It just becomes part of their normal life for a while.”

That father certainly agreed: It’s a small price to pay for a big, lifelong improvement.

● Challenge: Repair abnormal skull growth in infants whose skull plates fuse prematurely

● Approach: Remove a small strip of the fused plates, and shape the skull with a helmet

● Progress: The infant is home quickly, and the repaired skull looks perfectly normal

Medical illustrations by Tim Phelps, M.S., F.A.M.I., Associate professor and medical illustrator, Johns Hopkins Department of Art as Applied to Medicine; artwork copyright JHU 2008.
Patients with schwannomatosis face a double-whammy. Not only does the disorder produce debilitating pain caused by hundreds of schwann-cell tumors growing throughout the myelin sheaths around the nerves, but it is so rare that few neurologists or neurosurgeons have seen it. At the Johns Hopkins Comprehensive Neurofibromatosis Center, both types of specialists have come together to care for patients and find potential breakthrough treatments for these tumors and other forms of the peripheral nerve tumors known as neurofibromas.

Neuro-oncologist Jaishri Blakeley, director of the center, has been searching for a drug that can block the chemical messages on which the tumor cells are relying for growth. By examining the tumors removed from patients with neurofibromatosis type 2, she has already proved that experimental drugs are making their way in good concentrations into the tumors rather than being blocked as some drugs are by the “blood-nerve barrier”—a chemical defense analogous to the blood-brain barrier that makes it so difficult to get drugs into the brain.

The ability to assess a drug’s access to and activity in tumors following surgery can help to more quickly screen drugs to find the ones most likely to justify the substantial investment of a larger clinical trial. “It would be fantastic to hit on a cure right away,” says Blakeley. “It’s a giant step forward to eliminate those drugs that don’t work so we can move on to others.”

Another big breakthrough would be a long-sought-after means to quickly catch neurofibromas that are becoming malignant. To that end, neurosurgeon Allan Belzberg has been collaborating to apply an advanced MRI technique called neurography to spot these nerve malignancies. He’s also working in the laboratory to hunt down a biomarker for these tumors that would allow detection with a simple blood test.

Meanwhile, when a peripheral nerve tumor becomes malignant or impairing, Belzberg not only removes it, he surgically repairs damaged nerves by splicing in nerves from an arm or leg to restore some of the otherwise lost function. That’s a dual treatment not often available outside the center. “Losing the ability to flex an elbow can make an arm useless,” he says. “By repairing the damaged nerve or rewiring the system we can help recover much of that muscle control.”

Challenge: Catch and treat peripheral nerve tumors, especially malignant or painful ones

Approach: Splice in nerves to repair damage, find diagnostic tests and develop a drug cure

Progress: Muscle control can be restored, imaging is catching malignancies, drug screening is under way
At a special Johns Hopkins unit, patients can be seen repeating such mundane tasks as moving an arm or naming an object. In this seemingly trivial way, they are helping neurologist Nathan Crone gather information that could prove critical to their own quality of life—as well as to gain insights that could eventually lead to enormous advances in neuroscience. That’s because these patients, who suffer from epileptic seizures, have had their brains wired with electrodes that are recording the data Crone needs to safely treat their seizures as well as map the human brain. “These patients,” he says, “are helping science, so that science can, in turn, help them.”

Often the only way to relieve a patient of severe seizures is to surgically remove a part of his or her brain. But which part? To figure that out, surgeons implant a grid of several dozen electrodes over the surface of the cortex in the patient’s brain. For the next week, the patient performs simple motor, speech and memory tasks while the electrodes record the corresponding electrical activity in the brain and any seizure-related activity. “We can now see in unprecedented resolution where the brain is and isn’t active during each task,” says Crone. He and colleagues use the data to hunt down the small section of the patient’s brain most responsible for seizures and least tied to function. At the end of the week, that section is removed in surgery.

But in thinking about all the data accumulating across many patients, Crone realized he had a unique opportunity to derive general insights into which parts of our brains control what—that is, to create a map of the brain keyed to specific functions. Such a map could prove vital to treating other neurological problems as well as to improving learning and possibly to controlling prosthetic limbs with thoughts. And the electrical patterns Crone studies are already providing clues to how the brain encodes information. “If we can learn which signals carry the most important information, we could do an even better job of minimizing impairment when we remove tissue,” he says. That’s one way science could pay the patients with epilepsy back for sharing a precious glimpse into the inner workings of their brains.

**Challenge:** Surgically stop seizures and map brain function

**Approach:** Record brain activity with implanted electrodes and correlate it to tasks

**Progress:** Patients are being relieved of seizures with little impairment; the map is under way
New Approaches to Taming Seizures

Patients who have severe epileptic seizures often undergo the removal of a small section of brain suspected of being at the root of the problem. But that doesn’t always stop the seizures, and it’s not a good option if seizures originate in multiple regions or regions that control important functions. But some of these patients may have a new treatment option and better outcomes, thanks to Johns Hopkins neurosurgeons William Anderson and Frederick Lenz.

Anderson implants electrodes in patients’ brains that detect preseizure electrical activity among neurons—and then put out a short, mild blast of electricity that quiets the abnormal discharges. While sending in more electricity sounds as if it ought to make things worse, notes Anderson, it often stops a seizure cold. That could be because the stimulation changes the abnormal activity into a pattern of firing less likely to spread. “The neurons use up their energy when they fire, so they can’t create the spikes that can lead to a seizure,” he says.

In a clinical trial, the technique reduced seizures by an average of about 40 percent without impairing or even bothering patients. It may be even more effective, suggests Anderson, among patients whose seizures can be pinned down to specific areas of the brain. And some of these patients are the ones who aren’t good candidates for tissue removal. “This approach will be the next line of defense,” he says.

Whether the treatment is tissue removal or stimulation, results will be better when doctors can more accurately track down which brain regions lead to seizures and which control key functions. Standard recording and imaging techniques often show that multiple regions are active during a given event or task. “Some active regions may be important to a function, but others may not,” says Johns Hopkins neurosurgeon Frederick Lenz. Identifying which regions are actually the essential ones can be a big challenge.

To find out which regions matter most, Lenz is analyzing data from implanted electrodes to determine which pairs of regions tend to fire synchronously and which regions cause or drive activity elsewhere in the brain. The results may be useful in zeroing in on those areas that can be stimulated for effective treatment of seizures as well as for treatment of the tremors of Parkinson’s disease and chronic pain. “Stimulation is not always effective” he says, “and that may be because we’re applying it in the wrong places.”

- **Challenge:** Stop seizures without removing tissue
- **Approach:** Electrically stimulate brain cells, and identify key brain regions
- **Progress:** A big reduction in seizures, and new insights into which regions matter most

Electrodes implanted in a patient’s brain.
When Scientific Surprises Lead to New Drugs

Academic researchers are great at fundamental science, and pharmaceutical companies are great at developing drugs, but sometimes the two have trouble linking up. Some Johns Hopkins neuroscience researchers are closing that gap.

One of them is Barbara Slusher, who is leading a new drug discovery initiative at the Johns Hopkins’ Brain Science Institute focused on transforming Hopkins’ basic neuroscience discoveries into useful drugs for patients. Her multidisciplinary team is a collection of 20 biologists, chemists and pharmacologists, all with significant pharmaceutical drug discovery experience. “The researchers here at Hopkins are world-renowned, but their findings aren’t always translated into real-world medicine,” says Slusher.

Slusher’s experienced team has been on campus for only 18 months, but already their results are impressive. For example, the group is working with an amino acid called D-serine that Hopkins research showed stimulates glutamate receptors in the brain, decreasing schizophrenic symptoms. Unfortunately, the body quickly breaks down D-serine, requiring dangerously large doses for efficacy. The group’s solution: designing a molecule that slows the amino acid’s breakdown, allowing the dose to be reduced by 90 percent. Now the team is developing the drug combination for a clinical trial.

Although they are a brain-science-focused team, serendipity also led them to a cancer project. The group was working on a drug that blocks an enzyme called glutaminase—implicated in neurodegeneration—until new Hopkins research discovered that blocking the same enzyme may be even more effective at killing cancer cells. The latter is now the group’s focus. “It’s a great example of how research can start in one place and end up in another,” says Slusher.

Also taking a surprising and promising turn is research going on in the lab of Johns Hopkins neuro-oncologist John Laterra. Laterra has been working on ways to block the action of a molecule called c-Met, found on the surface of brain cells, which provides a foothold for a growth factor that promotes the aggressive brain tumor called glioblastoma. Partnering with two pharmaceutical companies, Laterra has helped develop a monoclonal antibody that seems to interfere with c-Met’s function, preventing the growth factor from doing its deadly job as a catalyst.

Now it turns out that c-Met may also be critical in providing glioblastomas with a pool of stem cells whose ability to change helps the tumors develop resistance to treatment. “Inhibiting this pathway will probably make the tumors more susceptible to other drugs,” says Laterra. It’s a big break that could ultimately save lives.

Challenge: Translate basic neuroscience research into drugs that help patients
Approach: Foster collaborations between basic researchers and experts in drug discovery
Progress: New candidate drugs that could help combat schizophrenia and brain cancer
A man in his early 20s issues a sentence of nine words. That’s not normally a noteworthy event, but for this young man it’s actually an extraordinary triumph. That’s because he has severe autism that until the age of 14 had left him unable to speak a word. “There’s no case in the literature of someone with autism acquiring speech so late,” says Barry Gordon, the Johns Hopkins neurologist who ran the therapy program that has given this person words and who is now extending his research in ways that could potentially help millions of others.

Gordon and his colleagues have long worked to find ways to unlock communication in low-functioning children and young adults with autism—a group that includes his own son, who Gordon says has been a big source of his inspiration. Standard behavioral therapy techniques, in which patients undergo intensive sessions of repeated prompts to perform certain tasks such as pointing to a picture of a named object, can be effective. But Gordon and his colleagues have been using additional techniques to try to improve on the more standard ones, hoping in part to unlock abilities that these children may have but simply can’t communicate. “It’s surprising how much some of these children know,” he notes. “They’re just trying to find a way to express it.” Gordon’s team has been using such methods as measuring pupil sizes, eye movements and brain electrical activity to help determine what these children know and what they don’t know. They also record therapy sessions and then pore over them for clues to what the subjects are trying to communicate and what methods seem to be helping or hindering them. “Very minor facial expressions can be very telling,” says Gordon.

Gordon is also trying to find ways to help others with impaired speech, including stroke victims. Among the new tools showing promise with research subjects is transcranial direct current stimulation, applying a very mild electric current to carefully chosen points on the scalp, a technique shown to sometimes boost learning in the brain. But in all cases, says Gordon, the most important thing is to keep working with those who face these challenges. “We think people just give up too often,” he says. “We don’t.”

**Challenge:** Enable young people with autism, and others with impairments, to speak

**Approach:** Shape sounds that subjects already make; mild electrical brain stimulation

**Progress:** Nonverbal children are showing surprising comprehension; one young man with no speech until age 14 is now talking understandably.

![tDCS illustration by Kimberly Battista (www.battistaillustration.com) and stimulations of current flow in the head by Dr. Rosalind Sadlier.](image-url)
Researchers have long believed they know what causes the devastating, little treatable and ultimately fatal damage to the brains of patients with amyotrophic lateral sclerosis (ALS), or Lou Gehrig’s disease. Namely, astrocytes—cells that support neurons in several ways—lose their ability to sweep away glutamate, a molecule that is used by the brain to transmit signals between neurons. The neurons end up swimming in glutamate, which in high concentrations damages them.

But neurologist Jeffrey Rothstein wondered if that was really the main problem. Rothstein, who heads the Brain Science Institute and the Center for ALS Research at Johns Hopkins, figured that if the astrocyte—glutamate transport mechanism goes awry in ALS, something else must be off too. After all, the countless chemical pathways in the body act together as a network, rarely working or malfunctioning entirely in isolation. And sure enough, he and colleagues found there was a mechanism that had been overlooked.

Neurons get energy from glucose provided by astrocytes. But they also get some energy from lactate, and the lactate, Rothstein’s team discovered, turns out to come not from astrocytes but from oligodendroglia, the cells that help make and maintain the fatty sheaths around nerve cells. This lactate-delivery process is much more important to the proper functioning of neurons than realized—and it breaks down in brains afflicted with ALS. “The literature was wrong,” says Rothstein. “We all thought ALS was solely a disease of astrocytes. But we really need to focus on what’s happening in the oligodendroglia.”

Rothstein and his colleagues have already looked at ways to try to restore the oligodendrogial lactate-production mechanism that’s broken in ALS, and in mice some early efforts have already shown promise in halting the progress of the disease. What’s more, Rothstein has collaborated with imaging researchers in working on an oligodendroglia-spotting technique that could provide a means for diagnosing and tracking ALS from its earliest stages. “We’ve never had a biomarker for ALS, and that’s been a big obstacle,” says Rothstein, who notes that the technique is now being tested in patients. “We now have an entirely new way of tackling ALS, and it’s come right out of left field.”
Attacking Two Brain Disorders on Multiple Fronts

Multiple sclerosis (MS), though usually not fatal, can be debilitating enough to rob even young people of the ability to lead productive, enjoyable lives. That keeps Johns Hopkins neurologist Peter Calabresi working hard on a two-pronged strategy to combat the disease, in which the body’s own immune cells attack the fatty myelin sheaths around parts of the cells in the brain and spinal cord.

One approach is to block the damaging immune cells in the brain—but without blocking all immune cells, which would leave the brain vulnerable to infections. Calabresi and colleagues have already identified a protein that, if targeted by a blocking agent, would stop all the MS-causing immune cells while leaving alone 90 percent of other immune cells. “That’s getting us much closer to the selectivity we need,” he says.

Meanwhile, Hopkins neurologist Carlos Pardo-Villamizar is investigating new strategies to fight transverse myelitis (TM), which produces many of the same symptoms as MS, though it’s caused by inflammation confined to the spinal cord. Working out of what was the world’s first dedicated TM center, Pardo-Villamizar is trying to find combinations of drugs that can suppress the immune system activity that causes the inflammation. He’s collaborating with colleagues to develop other strategies, including electrical stimulation of muscle groups and special exercises, to help patients recover more quickly from the impairments brought on by TM.

Also critical, he says, is finding new ways to tell the disorder apart from MS and other diseases that can seem similar. He and colleagues are currently hunting for proteins and antibodies in patients’ spinal fluid that can serve as biomarkers. “If we can find the fingerprints that tell us which disease we’re dealing with, we often know how to treat it,” he says.

Challenge: Find better treatments and diagnostic tools for multiple sclerosis and transverse myelitis

Approach: For MS, selectively block immune cells and promote repair to brain-cell sheaths; for TM, suppress inflammation and find telltale antibodies.

Progress: Potential drugs are showing early promise in MS, and new techniques are helping patients recover more quickly from TM
A High-Tech Way to Boost Stroke Recovery

Robots and video games probably aren’t the first things to come to mind when you think of strokes. But that may change if ambitious research by Johns Hopkins neurologist John Krakauer pans out. Krakauer is gathering evidence that a course of high-tech rehabilitation therapy, if applied quickly and intensively, can restore much of the function lost to a stroke. “There’s a limited window of time to act after a stroke,” he says. “Within it, we can get amazing degrees of recovery.”

The standard form of rehabilitation treatment for an acute stroke is two weeks in a rehabilitation unit for three hours of therapy a day, followed by a limited number of therapist visits to the home. “That’s too little, too late,” says Krakauer. “And it’s focused not on recovering lost function, but on compensating for it with remaining function.” Patients who lose the use of one arm, for example, are trained to rely more heavily on the other arm.

But neuroscientists know from animal data, notes Krakauer, that a great deal of function can be recovered by repeating tasks that rely on lost function at least 400 times—if the therapy is applied during the brief time after a stroke when the brain is more susceptible to changes. In humans, that window is three months. Ideally, stroke patients would be pushed to repeat critical tasks all day long by therapists. But since that would be too costly, Krakauer envisions placing patients in front of a special video game that prompts them to work on the needed tasks, assisted by a robotic system that ensures the motions are repeated correctly. The therapy would also include transcranial direct current stimulation, in which a mild electric voltage is applied to the scalp, and which has also been shown to boost learning.

Right now Krakauer is studying ways to use brain-imaging techniques to be able to spot those patients who can most benefit from this novel, intensive therapy. “These patients usually recover the least amount of function,” he says, “but with a robot and stimulation, we should be able to get improvement that goes far beyond what we usually see.”

---

Probing the Mysteries of Brain Injury and Sleep

The traumatic brain injury suffered by victims of blasts and car accidents can be challenging to assess and treat. That may in part be because of damage to the pathways along which different areas of the brain communicate—pathways that are largely mysterious because there has never been a good way for researchers to follow them. Now Johns Hopkins researcher John Desmond hopes to cast a light on these pathways with magnetic stimulation. “This will give us a chance to do the first neuroanatomical tracings of the injured human brain,” says Desmond.

Desmond is enlisting the help of transcranial magnetic stimulation (TMS), applied through a coil placed on the scalp. TMS can cause a specific region of the brain to briefly become more active, and that enhanced activity can be clearly imaged via fMRI—along with any other regions that light up in response. In this way, Desmond thinks he’ll be able to chart the paths of brain signals. Comparing the results from a traumatic brain injury patient with those of uninjured subjects could show that one or more of these pathways are damaged in the patient. “That could give us ideas about which areas and functions are most affected by the injury and guide us in treatment,” says Desmond. “And it might give us a good way to monitor progress.”

Insomnia may not seem quite as dramatic a problem, but Johns Hopkins neurologist Rachel Marie Salas...
thinks another type of brain stimulation might reduce the toll sleeplessness can take on patients’ daytime functioning. Even though insomnia is one of the conditions patients complain of most, says the sleep disorders specialist, “we don’t really have good evaluation and treatment strategies.”

To help clear up some of the questions, Salas is conducting a study in which both insomniacs and good sleepers learn a simple, single-task video game, and then take a two-hour nap while she monitors their brain waves via EEG. The key, she says, is that some of her study participants will also get transcranial direct current stimulation—a mild electric current applied to the scalp with electrodes—to see how it affects either group with the task or sleep. “We want to see if the stimulation can make a difference,” says Salas, “and we want to come up with better ways to evaluate people’s responses to different medications and other therapies.” It’s an idea worth sleeping on.

○ **Challenge:** Find the brain-pathway problems behind traumatic brain injury, and treat insomnia

○ **Approach:** Magnetic stimulation to reveal the pathways, and electrical stimulation to shed light on insomnia

○ **Progress:** Patient studies are planned for brain injury and will be starting soon for insomnia
The Johns Hopkins Departments of Neurology and Neurosurgery are here to collaborate with you at our locations throughout central Maryland.

**ONLINE:** For more information about our services, visit hopkinsmedicine.org/neuro

**TELEPHONE:**
- Adult Neurology 410-955-9441
- Pediatric Neurology 410-955-4259
- Adult Neurosurgery 410-955-6406
- Pediatric Neurosurgery 410-955-7337

**Locations**

**The Johns Hopkins Hospital**
600 N. Wolfe Street
Baltimore, MD 21287

**Johns Hopkins Bayview Medical Center**
4940 Eastern Avenue
301 Building, 3rd floor
Baltimore, MD 21224

**Johns Hopkins Health Care & Surgery Center at Green Spring Station**
10755 Falls Road
Lutherville, MD 21093

**Johns Hopkins Neurosurgery Suburban Hospital Outpatient Medical Center**
6420 Rockledge Drive
Bethesda, MD 20817
Referral Assistance

Physician-to-Physician
For urgent physician-to-physician referrals or consultations, call the Hopkins Access Line (HAL) at 1-800-765-5447.

For Patients Outside of Maryland
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. Out-of-state patients can contact Johns Hopkins USA at 1-855-695-4872 (1-855-MY-JHUSA).

For Patients Outside of United States or Non-English Speaking Patients
Johns Hopkins Medicine International (JHI) arranges all aspects of a patient’s medical visit for those traveling from outside of the United States, paying special attention to personal, cultural and travel-related needs. Our caring staff can arrange consultations, remote medical second opinions or treatment plans with the most appropriate specialists. JHI also provides language interpretation, financial counseling, assistance with travel arrangements and anything else to help make Johns Hopkins feel as close to home as possible. For more information, call +1-443-287-6080.