

Physician Update

NEWS FOR PHYSICIANS FROM JOHNS HOPKINS MEDICINE

FALL 2009

Opening a New Path for Cardiac Stem Cells

By the time Bill Beatty made it to an emergency room, he was already several hours into a major heart attack. His physicians performed a series of emergency treatments that included an intra-aortic balloon pump, but the 57-year-old engineer's blood pressure remained dangerously low. The cardiologist called for a helicopter to transfer him to Johns Hopkins.

It was fortuitous timing: Beatty was an ideal candidate for a clinical trial and soon received an infusion of stem cells derived from his own heart tissue, making him the second patient in the world to undergo the procedure.

Of all the attempts to harness the promise of stem cell therapy, few have garnered more hope than the bid to repair damaged hearts. Previous trials with other stem cells have shown conflicting results. But this new trial, conducted jointly with cardiologist Eduardo Marbán at Cedars-Sinai Medical Center in Los Angeles, is the first time stem cells come from the patient's own heart.

Cardiologist **Jeffrey Brinker**, a member of the Hopkins team, thinks the new protocol could be a game-changer. That's based partly on recent animal studies in which scientists at both institutions isolated stem cells from the injured animals' hearts and infused them back into the hearts of those same animals. The stem cells formed new heart muscle and blood vessel cells. In fact, says Brinker, the new cells have a predetermined cardiac fate. "Even in the culture dish," he says, "they're a beating mass of cells."

What's more, according to Hopkins lead investigator **Gary Gerstenblith**, the animals' hearts in these studies showed "a significant decrease in relative infarct size," shrinking by about 25 percent. Based on those and earlier findings, investigators were cleared by the FDA and Hopkins' Institutional Review Board to move forward with a human trial.

In Beatty's case, Hopkins heart failure chief **Stuart Russell** extracted a small sample of heart tissue and shipped it to Cedars Sinai, where stem cells were isolated, cultured and expanded to large numbers. Hopkins cardiologist **Peter Johnston** says cardiac tissue is robust in its ability to generate stem cells, typically yielding several million transplantable cells within two months.

When ready, the cells were returned to Baltimore and infused back into Beatty through a balloon catheter placed in his damaged artery, ensuring target-specific delivery. Then the watching and waiting began. For the



Among those moving the trial forward are cardiologists Peter Johnston and Jeffrey Brinker.

Hopkins team, Beatty's infarct size will be tracked by imaging chief **Joao Lima** and his associates using MRI scans.

Now back home and still struggling with episodes of compromised stamina and shortness of breath, Beatty says his Hopkins cardiologists were "fairly cautious" in their prognosis, but he'll be happy for any improvement.

Nurse coordinator Elayne Breton says Beatty is scheduled for follow-up visits at six months and 12 months, when they hope to find an improvement in his heart's function. But at least one member of the Hopkins team was willing to acknowledge a certain optimism. "The excitement here," says Brinker, "is huge."

The trial is expected to be completed within one to two years.

CADUCEUS Trial Eligibility

To be considered a candidate for the study of cardiosphere-derived autologous stem cells to improve ventricular function following a myocardial infarction (CADUCEUS), patients must have had a myocardial infarction within the prior four weeks and been treated with successful coronary angioplasty and stent placement. In addition, the left ventricular ejection fraction must be between 25 percent and 45 percent. To refer a patient for consideration for the study, call Gary Gerstenblith at 410-955-6834 or Peter Johnston at 410-550-5966.

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The following clinical trials are actively recruiting patients.

Carotid Artery Disease

Mahmoud Malas is the Johns Hopkins principal investigator for the ACT 1 study, a multicenter, prospective, randomized trial comparing the gold standard carotid endarterectomy versus minimally invasive carotid stenting under cerebral protection to treat carotid artery stenosis and prevent stroke. Info: 410-550-1355

Heart Failure

John Conte, Stuart Russell and Ashish Shah are the principal investigators of an FDA trial evaluating the efficacy of the HeartWare left ventricular assist device for bridge to transplantation. Info: Dzifa Dordunoo, 410-955-3597, edordun1@jhmi.edu

Marfan Syndrome

Luca Vricella is the Johns Hopkins principal investigator of a multicenter study evaluating and comparing operative outcomes of the aortic valve-sparing and aortic valve-replacement surgical interventions in adult and pediatric patients with Marfan syndrome. Info: Kimberly Behrens, 410-502-1914, kbehren1@jhmi.edu

Metabolic Syndrome

Pamela Ouyang is the principal investigator of a placebo-controlled trial studying the effect of a range of doses of an oral antioxidant, alpha lipoic acid, on levels of oxidative stress and inflammation in patients with glucose intolerance/diabetes, hypertension, high lipids and moderate obesity. Info: Jeanne Wingo, 410-550-4278, jwingo@jhmi.edu

Multiple Sclerosis

Peter Calabresi is the principal investigator for Relapsing Remitting Multiple Sclerosis (RRMS): A Combination Trial of Copaxone Plus Estriol in Relapsing Remitting Multiple Sclerosis (RRMS) (Estriol in MS). The multicenter trial is evaluating whether oral treatment with estriol, the major estrogen of pregnancy, decreases relapses in relapsing remitting multiple sclerosis when used in combination with injectable Copaxone. Info: Peter Calabresi, Stephanie Syc, ssyc1@jhmi.edu, 410-502-2488

Parkinson Disease

Ted M. Dawson is the principal investigator on a study of the effects of coenzyme Q 10 in patients diagnosed with Parkinson disease within the last five years who are not currently being treated for it. Info: Becky Dunlop, 410-955-8795 or rdunlop@jhmi.edu

Peripheral Arterial Disease

Elizabeth Ratchford is the local principal investigator of the CLEVER study, a prospective, randomized multicenter clinical trial comparing the benefits of supervised exercise, endovascular revascularization and optimal medical care in adults age 40 and older with intermittent claudication due to aortoiliac peripheral arterial disease. Info: Elizabeth Ratchford, 410-616-7225; eratchf1@jhmi.edu

Sphincter of Oddi Dysfunction

Anthony Kalloo is the Johns Hopkins principal investigator for the EPISOD study (Evaluating Predictors & Interventions in Sphincter of Oddi), a multicenter phase III clinical trial of endoscopic sphincterotomy as treatment for adults with type III sphincter of Oddi dysfunction. Adults age 18 to 65 with persistent or recurrent abdominal pain following cholecystectomy may be eligible. Info: Laurie McClelland, 410-955-3822 or <http://hopkins-gi.org/episod>.

Curing the Nonacid Reflux Cough

The 57-year-old had battled a severe cough accompanied by reflux for five years and had undergone various tests to check for asthma or allergy correlations, all to no avail. When she was referred to gastroenterologist **John Clarke**, director of esophageal motility at The Johns Hopkins Hospital, he was determined to find the cause of her cough.

What makes chronic coughs so challenging, Clarke says, is that they can be due to anything from asthma and lung disease to gastroesophageal reflux disease or thyroid disorders. After ruling out just about all of these, Clarke was left with the high probability that acid reflux was the underlying culprit.

After four months of acid-suppression treatment didn't alleviate the patient's symptoms, Clarke turned to combined pH/impedance, a test that measures the flow, consistency and extent of reflux. The impedance catheter, which contains flow-measuring metal rings, is placed for 24 hours after localization of landmarks by high-resolution esophageal manometry. Unlike standard catheters that measure only pH, the impedance catheter also detects both acid and nonacid reflux.

In Clarke's patient, the test confirmed the presence of nonacid reflux disease and helped clarify the treatment options: "We either wanted to try to block the reflux with medical therapy," he says, "or we could do surgery."

Clarke first chose baclofen, a muscle relaxant commonly used to treat spasticity that's been shown to decrease the number of daily reflux events (Clarke's patient



John Clarke

was experiencing up to 96 a day.) The downsides are frequent daily administration and side effects that include dizziness and weakness.

After a few weeks, the patient's cough did improve, and the number of reflux episodes decreased, but she also became chronically tired and weak. Only then did Clarke recommend a Nissen fundoplication to tighten the junction between the sphincter and the stomach—and basically cut off the reflux. Two weeks after the laparoscopic procedure, the patient's cough began improving significantly.

Though Clarke might have gone straight for surgery, "you want to be as certain as possible," he says, "that there's going to be a benefit." And for that, he credits the pH impedance system: "Without it, we wouldn't have gotten the information we needed to recommend surgery." ■

☎ 410-955-4166 to refer a patient.

A Re-Boot for Vesicoureteral Reflux

It's rare for an entire specialty to consider overhauling its approach to a time-honored treatment protocol, but pediatric urologist **Ranjiv Mathews** says the data leave no choice. He and about 30 other U.S. experts pored over mixed outcomes and debated study plans for more than 18 months. All agree it's time for new answers.

The condition at hand is vesicoureteral reflux, the urinary tract disorder that afflicts more than 1 in 10 people, most under age 12. At VUR's most advanced stage, urine can flow back into the kidneys, eventually scarring them with infection and sometimes escalating to the need for a kidney transplant. Mathews says about half the children who come to Johns Hopkins with urinary tract infections are confirmed as having VUR. His group treats about 150 of them every year.

The trouble, says Mathews, is that he and others now suspect that they could be managing the condition much better. In mild cases, doctors have used prophylactic antibiotics to reduce infections, hoping the condition resolves spontaneously. In the more significant grades of VUR cases, surgeons reroute the patient's ureters. But the interventions can be costly and aren't always effective. Even the surgical repairs—effective in preventing VUR—don't always reduce the incidence of infections and scarring. And, says Mathews, recent data show that antibiotics may not prevent scarring and infections.

Several years ago, the National Institutes of Health demanded a new look and in 2007 backed a national study (RIVUR, for Randomized Intervention for VUR) that now involves 20 centers across the coun-

try. It will start with the antibiotics question and then proceed to others, including gauging surgical outcomes and hunting for a suspected genetic component. "We really should know more about this," says Mathews, "because it not only has an impact on this generation, but an even bigger impact on future generations of children."

RIVUR Eligibility

Study candidates must be 2 months to 6 years of age, have been diagnosed with first or second febrile or symptomatic urinary tract infection within 112 days of randomization, exhibit grade I-IV VUR based on radiographic VCUG performed within 112 days of diagnosis of index UTI, and have undergone appropriate treatment.

☎ 410-955-3693 to refer a patient.

A Current Approach to Depression

A transcranial magnetic stimulation (TMS) system was recently unpacked in Johns Hopkins Hospital's Meyer 3 suite, where it's become the centerpiece of a new patient service. Out of the box in ways more than literal, TMS offers an FDA-approved alternative therapy for major depression in adults who've given antidepressants a valiant trial and not been helped.

TMS induces weak electric currents that excite targeted sites in the brain. Why that can ease depression is far from clear, says psychiatrist **Irving Reti**, who directs Hopkins Psychiatry's new Brain Stimulation Program. But having a noninvasive treatment that doesn't have whole-body effects is reason enough for making it available, he says.

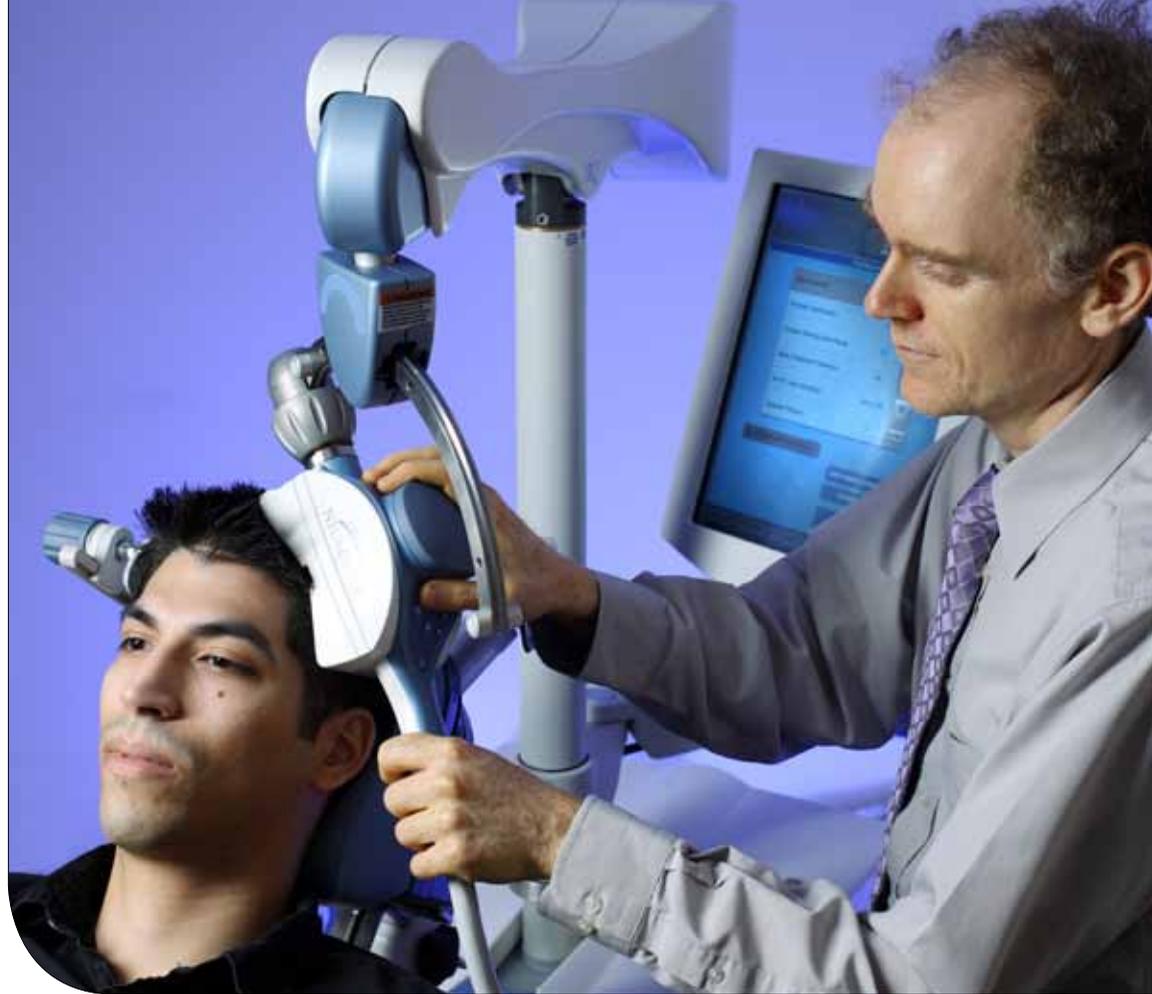
"The main question," Reti explains, "is efficacy." With TMS, relief from depression appears variable. Some patients report that their depression lifts completely; others see little effect. The benefit averages out, according to some 30 trials conducted worldwide, to about a quarter of patients reporting significant relief. Then

follow-up antidepressants sustain it.

"There's a real need to be able to identify who's most likely to be helped," Reti says. The fact that TMS takes a time commitment—the recommended protocol is 40 minutes daily, five days a week for four to six weeks—underscores the need.

Safety, however, isn't in question. "The risk of seizures, which might be a concern, is exceedingly low," Reti adds. Even more important to patients is the lack of the cognitive side effects that can occur with electroconvulsive therapy. "Aside from mild headache in some," Reti says, "patients don't have complaints."

This could make TMS a good option for people who can't tolerate antidepressant medications or could be endangered by drug interactions. "We may also find out it's useful in pregnancy," Reti adds.



When antidepressants fall short, says Irving Reti, TMS may help.

The way is open, then, for clinical trials. As a start, the Hopkins group has two under way. One will study TMS in teens age 15 to 18 with entrenched depression. The recent warnings about antidepressants in this group, Reti says, spur that trial on.

A second study—with adults—uses a variation of TMS that penetrates deeper brain. Because the technique's electromag-

net is open to creative design, an experimental version of TMS can reach beyond the 3 centimeters of prefrontal cortex that standard therapy touches. Exciting deeper orbitofrontal cortical pathways that control pleasure and motivation may make TMS more effective, Reti says. ■

☎ 410-955-5212 to refer a patient. For research information: 410-614-1732.

Teamwork Versus Pancreatic Cancer

The 43-year-old had been told by doctors in upstate New York that her pancreatic cancer was too extensive for removal, even after they had performed nearly 12 hours of surgery. But when the anxious woman called **Richard Schulick** for a second opinion in late February 2007, the chief of Johns Hopkins' Division of Surgical Oncology said, "Why don't you come down to Balti-

more and meet with our pancreatic cancer group?"

The woman soon joined six other pancreatic cancer patients who'd arrived for a ritual that group director **Joseph Herman** and nearly 20 other specialists perform each Tuesday. After this team of oncologists, radiologists, gastroenterologists, geneticists, pain specialists, immunologists and surgeons review the patient histories, documents and scans in each case, they

recommend a consensus plan of action. Many of the patients from that day were given new hope.

In this particular patient's case, Schulick and the team first wanted a course of radiation and chemotherapy to reduce the tumor to a manageable size. If the tumor's growth halted, it would raise Schulick's confidence that surgically removing the mass would be a viable answer. After undergoing the prescribed treatment in her home state, the patient returned to Baltimore in the spring. The tumor had responded. It was smaller and potentially removable. Schulick told her it was a go.

He even addressed the issue that had dissuaded the surgical team in New York. While Schulick agreed that the tumor's involvement with the portal vein posed a risk of provoking a serious bleed, he and his team could resect and replace that vein if necessary.

In the operating room, Schulick and his team of seven found the patient's pancreatic tissues typically scarred and toughened from the chemo and radiation

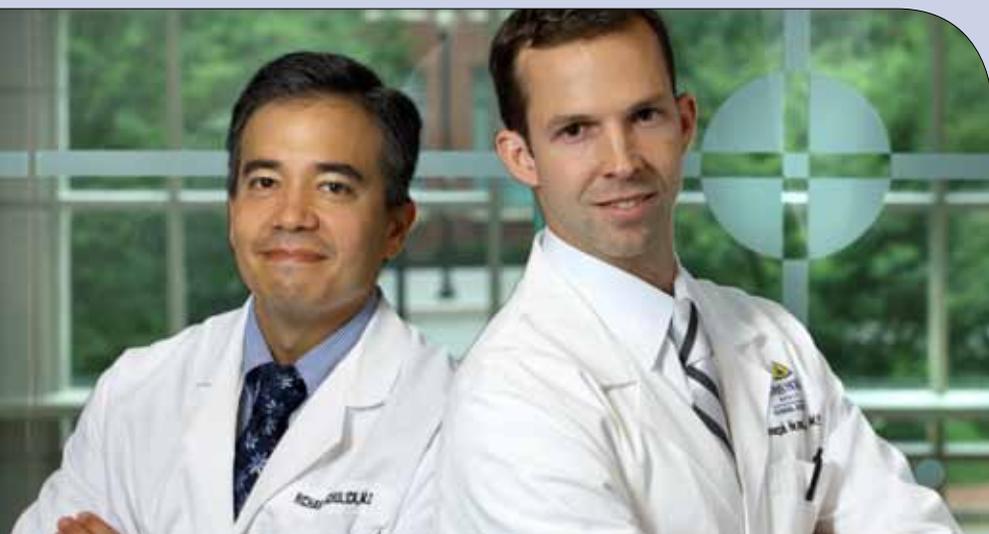
treatments. Even so, Schulick was able to perform a Whipple procedure, completely removing the cancer and the surrounding lymph nodes without any undue bleeding. Now two years post-op, the patient remains cancer-free and has returned to work.

Schulick sees her case as but one of many examples of his group's more aggressive attack on the pancreatic cancer problem. He says the concerted approach has helped him and other colleagues extend the lives of a growing number of pancreatic cancer patients, and he believes future outcomes data will document the progress. At 350 pancreatic resections last year, Schulick notes, Hopkins leads the nation.

Though surgical techniques have changed little in recent years, he says, "we now know how to better select those whom we can help. We live, eat and breathe the destruction of pancreatic cancer. Unless we throw everything at it, we will never beat it." ■

☎ 410-933-7262 to refer a patient.

Richard Schulick and Joseph Herman: "If we are going to make progress, this is the model to do it."



When Tumors Attack the Spine

Fifteen years ago, only about one out of 10 spinal tumor patients was a candidate for surgery, says **Ziya Gokaslan**. Today, he estimates, that figure is eight or nine times greater. The reason: innovations in surgery.

“We didn’t have the approaches needed to access the tumor,” says Gokaslan, director of the Johns Hopkins Spine Center. Moreover, surgeons were severely limited in their ability to reconstruct the spine.

Gokaslan and his colleagues treat both patients with extrinsic tumors, which arise from the bone or soft tissue of the spinal column; and those with the less common intrinsic, or intramedullary, tumors, those that originate from the spinal cord itself.

The surgical team first removes any segment of the spine bone that blocks access to the tumor. They then use microsurgical techniques to remove the tumor. In some cases, the team uses a laser and ultrasonic aspirator to vaporize part or all of the tumor. Throughout the procedure, the patient’s spinal cord function is constantly monitored through electromyography, motor evoked potentials, or somatosensory evoked potentials. “If we see changes in these recordings, then we make a decision as to whether it’s safe to proceed,” says Gokaslan.

If a portion of spine has been removed, reconstruction is the next step. Spinal tumors can range from a few centimeters in length to the size of a watermelon, and in the latter case, the reconstruction can be highly complex. “Fifteen years ago,” notes Gokaslan, “outside of a few screws and a rod, we didn’t have anything to reconstruct the spine.” Today, they’re rebuilding spines with titanium cages, plates, spacers and other implants.

Among the particularly challenging forms of spinal tumor are those that grow on the spinal cord. Neurosurgeon **George**



Ziya Gokaslan and George Jallo: no strangers to challenging cases.

Jallo specializes in such cases. Many of his patients have been told that their case is inoperable. Last year, for example, he cared for a 17-year-old who had the extremely rare spinal tumor known as an ependymoma. Doctors at the boy’s local hospital had concluded that surgery to remove the tumor would be too risky. They administered radiation therapy instead, but the tumor continued to grow. “He then had surgery here,” says Jallo, “and we were able to remove the entire tumor without any new deficits, and he is doing well.”

A surgeon’s reluctance to operate in this vulnerable region is understandable, says Jallo. “The margin of error is on the order of millimeters.” But with a practiced team of specialists, those risks are significantly reduced. The Johns Hopkins Spine Center is one of a handful of places that specializes in spine tumor surgery, says Jallo.

Still, even with a dedicated team of specialists, any surgery on the spine involves a degree of risk. So both Gokaslan and Jallo in their research labs are searching for less invasive alternatives. Instead of a complete surgery, for example, one option is to make a small incision and apply a chemotherapeutic agent near the tumor site, an approach they are testing in animal models.

“We haven’t found a cure yet,” says Jallo, “but we have promising results.”

☎ 410-955-4606 to refer a patient.

Your Vital Links

Johns Hopkins Medicine offers the following resources for you and your patients.

Hopkins Access Line (HAL)
Physician-only line for consultations, referrals and patient transfers
1-800-765-5447 (Continental United States)
410-955-9444 (Baltimore area and international calls)

Online Referral Directory
Find a Hopkins physician by name, specialty and more
hopkinsmedicine.org/doctors

Referring PhysicianWEB
Secure site for viewing your patients’ information
410-502-2737
1-800-759-7734
JHMCares@jhmi.edu

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Jhintl.net

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PhysicianUpdate

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This newsletter is published for the Johns Hopkins Clinical Practice Association by Johns Hopkins Medicine Marketing and Communications

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