
MEDICAL DEVICE DAILY™

THE DAILY MEDICAL TECHNOLOGY NEWSPAPER

THURSDAY, APRIL 2, 2009

VOL. 13, No. 62

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New computer system to aid in artificial pancreas development

By AMANDA PEDERSEN

Medical Device Daily Staff Writer

Scientists are getting closer to developing an artificial pancreas for patients with diabetes and a new computer-simulated system created by California researchers should bring the artificial pancreas even closer to the market.

The system, created by researchers at the **University of California at Santa Barbara, Sansum Diabetes Research Institute** (Santa Barbara) and **Stanford Medical Center** (Palo Alto), is designed to help scientists evaluate an investigational artificial pancreas comprised of an insulin pump and a continuous glucose monitor. Research about the system was published in this month's issue of *Diabetes Technology & Therapeutics*.

Specifically, the investigational artificial pancreas is comprised of the OmniPod Insulin Management System from **Insulet** (Bedford, Massachusetts) – including the
See Pancreas, Page 6

New in basic science

'Counter-intuitive' cleansing of blood uses magnetism vs. sepsis

By DON LONG

Medical Device Daily National Editor

Magnetism is pretty interesting stuff, says Don Ingber, MD, PhD, a professor at Harvard Medical School and Director of Harvard's new Wyss Institute for Biologically Inspired Engineering. "It's behind all kinds of tricks when you're a kid. And it's really intriguing to see the techniques and capabilities it has enabled, that you might not have expected."

Ingber, his associate Chong Yung, PhD and their collaborators at **Children's Hospital Boston** (Boston) and **Draper Laboratories** (Cambridge, Massachusetts) are pursuing one of the more unexpected and intriguing capabilities of magnetism – along with an unexpected feature of microfluidic technology. In using these to perform a kind of disappearing act in the blood, they aren't just playing around.

See Magnetism, Page 7

Stryker loses PMA bid for OP-1 putty in committee

By MARK McCARTY

Medical Device Daily Washington Editor

GAITHERSBURG, Maryland – **Stryker** (Kalamazoo, Michigan) has had its share of regulatory headaches, including a December class I recall of cranial implants and a warning letter issued last year for distribution of the company's OP-1 Implant, a bone morphogenic protein product without study site approval. The company had to deal with more bad news Wednesday in the form of a decision by an FDA advisory committee to recommend that the agency not approve the PMA for its other bone morphogenic protein, the OP-1 Putty.

Stryker picked up a license for the OP-1 line of products from **Curis** (Cambridge, Massachusetts) in December 2007 (*Medical Device Daily*, Jan. 2, 2008). The agreement between Stryker and Curis entailed an initial payment of \$1 million and as much as \$41 million in royalty payments should the OP-1 products hit unspecified sales figures. Both OP-1 Putty and the OP-1 implant consist of the bone morphogenic pro-
See Stryker, Page 8

Cochlear implants have yet to become mainstay solution

By LYNN YOFFEE

Medical Device Daily Staff Report

Technology has been relatively slow to conquer a problem that affects millions of people worldwide: hearing loss and deafness. Although 36 million American adults report some degree of hearing loss, only one out of five people who could benefit from a hearing aid actually wears one, according to the **National Institute on Deafness and Other Communication Disorders** (NIDCD; Baltimore, Maryland).

Ideally, most people would prefer a device that's not visible, but the most advanced type of hearing aid, cochlear implants, are reserved for people with profound hearing loss or total deafness. Yet these devices aren't entirely implanted and only a handful have come on the market around the world since the first one was approved two decades ago, each of which has been somewhat fraught with difficulties along the way.

"Cochlear implants have two major disadvantages,"

See Implants, Page 9

INSIDE: ICF CLOSING ITS \$155 MILLION BUY OF MACRO INTERNATIONAL.....2
IRIS DOES NOT MAKE CASE FOR IMMEDIATE ICD IMPLANTATION AFTER MI3



*Deals roundup***ICF closes its \$155 million buy of Macro International****A Medical Device Daily Staff Report**

ICF International (Fairfax, Virginia) reported that it has closed on the acquisition of **Macro International** (Calverton, Maryland), an advisory, implementation, and evaluation services firm providing research-based solutions to U.S. federal government agencies in health and other areas. The purchase price was about \$155 million.

McGrath North Mullin & Kratz, and Arent Fox acted as ICF's legal counsel on the transaction. RSM McGladrey, conducted financial and tax due diligence.

Macro provides research and evaluation, management consulting, marketing communications, and information services to key agencies of the federal government.

ICF partners with government and commercial clients to deliver professional services and technology solutions in the energy and climate change; environment and infrastructure; health, human services, and social programs; and homeland security and defense markets.

In other dealmaking news:

- **Mednax** (Fort Lauderdale, Florida) reported that it has completed two separate physician group practice acquisitions, a neonatal group practice based in the Hampton Roads region of Virginia, and a pediatric cardiology practice serving patients in El Paso, Texas.

The physicians joining as a result of both transactions will practice as part of Mednax's Pediatrix Medical Group, a national medical group.

Hampton Roads Neonatology (Hampton Roads, Virginia) includes three physicians and six nurse practitioners who staff the Level III neonatal intensive care unit (NICU) and well-baby nursery at **Riverside Regional Medical Center** (Newport News, Virginia). Annual patient volume is about 7,000 NICU patient days and 8,000 newborn nursery patient days.

Today's MDD food for med-tech thought

"I think it's nice for [FDA] to see everything operating as one . . . it really helps to have everything in one system that we can test the whole system. You don't want to have a system that the components work but when you plug them all together they don't work and that is one of the concerns of the FDA . . . what happens when they start communicating together?"

– Howard Zisser, MD, director of clinical research and diabetes technology at the Sansum Diabetes Research Institute, discussing a new system that provides a testing platform, prior to patient trials, to fully verify and validate that an artificial pancreas can efficiently operate in the variety of conditions reflective of a large group of patients with the disease, "New computer system to aid in artificial pancreas development," pp. 1, 6.

Mednax also completed the acquisition of **Schuster Heart Center** (El Paso, Texas), a pediatric cardiology practice, effective Feb. 27.

Jeffrey Schuster, MD, is the founder and sole physician in the practice, which provides a range of cardiology services to pediatric patients, as well as fetal echocardiography services to patients throughout El Paso. Schuster has been providing patient care services in El Paso since 1990.

Mednax paid cash for the practices, which are expected to contribute immediately to the company's earnings. No additional terms of the transaction were disclosed.

Mednax is a national medical group that comprises what it terms the nation's leading provider of neonatal, maternal-fetal and pediatric physician subspecialty services as well as anesthesia services.

- **Tenet Healthcare** (Dallas) reported that company subsidiaries have completed the previously disclosed sales of **USC University Hospital** and **Kenneth Norris Jr. Cancer Hospital** to the **University of Southern California** (all Los Angeles) (*Medical Device Daily*, Feb. 11, *See Deals, Page 6*)

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*ACC notebook***IRIS does not make case for immediate ICD implantation after MI****A Medical Device Daily Staff Report**

Results from the IRIS (Immediate Risk Stratification Improves Survival) clinical trial, supported in part by **Medtronic** (Minneapolis) were presented this week at the Annual Scientific Session of the **American College of Cardiology** (ACC; Washington).

The results showed that sudden cardiac death in a specific subset of immediate post-myocardial infarction (MI) patients was statistically significantly reduced with implantable cardioverter-defibrillator (ICD) therapy. However, in this narrowly defined patient population, ICDs did not reduce mortality from all causes, as all causes are not treatable by ICDs, Medtronic said.

ICDs are 98% effective at terminating the dangerous heart rhythms that can lead to sudden cardiac death, but are not currently indicated for use in immediate post-MI patients. The IRIS trial sought to determine if survival amongst a subset of post-MI patients who were at high risk for sudden cardiac death could be improved by ICD therapy received in the first 31 days after a heart attack.

The trial compared outcomes for patients who received an ICD within a month of a heart attack to patients treated with standard medical therapy alone.

There were fewer sudden cardiac deaths in patients who got an ICD in the days following a heart attack, but that was counterbalanced by an increase in non-sudden cardiac deaths, according to authors of the study.

"Based on these findings, routine ICD implantation after [heart attack] cannot be recommended at this time," study author Dr. Adnan Chhatiwalla of the **Cleveland Clinic** said in a summary of the trial.

Patients who received an ICD in the Iris study were at high risk for sudden cardiac death, which can result from the onset of an abnormal heart rhythm. But the results for about 900 patients treated in European hospitals found no difference in the primary endpoint of all-cause mortality between groups at three years.

A significant percentage of people who survive a heart attack will ultimately die from a dangerous heart rhythm originating in the lower chambers of the heart, Medtronic said. About 15% will die in the first weeks, and an additional 10% during the first year.

"Medtronic is committed to developing an evolving base of clinical evidence critical to scientific advancement and medical practice," said David Steinhaus, MD, medical director of the Cardiac Rhythm Disease Management business at Medtronic. "The IRIS trial is another example of our efforts to identify the patients who will benefit most from our life-saving and life-improving therapies."

The company noted that the IRIS results do not conflict with previous data that informed current evidence-based

treatment guidelines which showed that use of ICDs in a more broadly defined range of post-MI patients (those who received ICD therapy at least 40 days after experiencing a heart attack) reduced all-cause mortality by 31%. Current medical guidelines recommend ICD therapy for post-MI patients with an ejection fraction – a common measure of the heart's pumping function – of 35% and below, and after at least 40 days have passed since their heart attack.

In other ACC news:

- **Impulse Dynamics** reported findings from the FIX-HF-5 study of its Optimizer system.

The company noted that previous studies have demonstrated safety and efficacy of the Optimizer system's cardiac contractility modulation (CCM) signals when applied for three months. The FIX-HF-5 study was designed to test the longer-term effects in the largest randomized study to date.

CCM therapy is a new treatment for patients with heart failure. Unlike electrical signals delivered by other cardiac devices, such as pacemakers and implantable defibrillators, CCM signals do not initiate a heartbeat. Rather, CCM signals are intended to modify heart cell function in a manner that improves the strength of the heart muscle, therefore potentially enhancing the heart's overall pumping ability. CCM is designed to increase the forcefulness of the heart's pumping action rather than initiating a new contraction.

The study met its primary safety endpoint, which was a noninferiority demonstration of the composite of all-cause mortality and all-cause hospitalizations. In terms of efficacy, the results showed that, compared to the control group, patients treated with CCM signals over the other group had significantly improved exercise tolerance as judged by an increase in peak oxygen uptake ($p=0.02$) and an improvement in quality of life as judged by a reduction in the Minnesota Living with Heart Failure score ($p<0.0001$).

The results did not, however, meet the study's overall primary efficacy endpoint demonstrating improvement in ventilatory anaerobic threshold, though that endpoint was met in a less sick subgroup of the patients.

"We are pleased to report these longer term data that add to the growing wealth of knowledge showing the potential of CCM as a therapy for heart failure patients with no other options," said William Abraham, MD, professor of internal medicine and director of the Division of Cardiovascular Medicine, **Ohio State University Medical Center** (Columbus).

- In a subgroup representing the less sick half of the study population (NYHA Class III with ejection fraction 25% and above), the study found even greater improvements not only in peak VO_2 ($p=0.001$) and quality of life ($p=0.003$), but also in the primary endpoint of ventilatory anaerobic threshold ($p=0.03$). These effects were largely maintained at twelve months as well.

"This subgroup of the less severely impaired patients appeared to demonstrate an overall greater response rate

See ACC, Page 5

Agreements/contracts**Altea to get up to \$46M
in transdermal patch deal****A Medical Device Daily Staff Report**

Altea Therapeutics (Atlanta) reported that it has entered into an agreement with **Eli Lilly and Company** (Indianapolis) and **Amylin Pharmaceuticals** (San Diego) to develop and commercialize a daily transdermal patch delivering sustained levels of exenatide using the Altea's PassPort Transdermal Delivery System in a deal valued at up to \$46 million.

Altea, supported by Lilly and Amylin, recently completed an initial Phase 1 clinical study of the exenatide transdermal patch in people with Type 2 diabetes.

The exenatide transdermal patch is an investigational product designed to be applied once per day to provide sustained levels of exenatide for people with Type 2 diabetes. The potential benefits for patients from the exenatide transdermal patch include eliminating injections, which may increase therapy compliance.

Under terms of the agreement, Altea has granted Lilly and Amylin exclusive worldwide rights to develop and commercialize transdermal exenatide using PassPort Transdermal Delivery System. Lilly and Amylin will fund all product development, manufacturing, and commercialization activities for the product.

Altea will receive from Lilly and Amylin an upfront license payment and may receive clinical, regulatory and sales milestones of up to \$46 million, and royalties on future product sales. As part of the agreement, an equity investment in Altea Therapeutics is included.

"This agreement continues the validation of the Altea Therapeutics transdermal patch technology for medicines that currently can be administered only by needle injection or infusion, including water-soluble proteins, carbohydrates, and small molecules," said Eric Tomlinson, PhD, DSc, president/CEO of Altea. "We believe the diabetes care experience of Lilly and Amylin, combined with the transdermal expertise of Altea Therapeutics creates an excellent partnership for the potential development of the world's first transdermal GLP-1 receptor agonist, transdermal exenatide."

"The agreement to develop a transdermal patch for exenatide is aimed at responding more broadly to the needs of the patients we serve by offering more treatment choices, such as the Altea Therapeutics non-injectable delivery option, for this important medicine," said Orville Kolterman, MD, senior vice president of research and development at Amylin.

In other agreements and contracts news:

- **iMedica** (Dallas) has become a member benefit partner of **Colorado Medical Society** (CMS; Denver), the state's largest physician-based association representing more than 7,000 members. The relationship comes on the heels of the \$19 billion in upcoming federal stimulus funds

for health information technology, as well as a national commitment to provide everyone in the U.S. with an electronic health record (EHR) by 2014. The partnership also reinforces Colorado's priority to support the sharing of electronic health information across organizations.

As part of the terms of the agreement, CMS member physicians will receive preferred pricing on all iMedica products, as well as the opportunity to participate in live educational seminars designed to highlight the benefits, efficiencies and improved functionality that an EHR and practice management (PM) solution can bring to a medical practice.

- **Amerinet** (St. Louis), a national healthcare group purchasing organization (GPO), reported the renewal of its agreement with **Shriners Hospitals for Children** (Tampa), which uses Amerinet's national portfolio of contracts and Total Spend Management business intelligence solutions to help manage its members' combined annual spend. The Shriners Hospitals for Children system represents several facilities throughout the U.S.

Specific benefits available to Shriners Hospitals for Children include contracts specially negotiated for system members, discounted pricing for all facility types, enhanced tier discounts for aggregated volume and customized educational solutions, through Amerinet's educational division, Inquisit.

- **Premier Purchasing Partners** (San Diego) reported that new agreements for medical lasers and light based systems have been awarded to **Lumenis** (Santa Clara, California) and **SSI Laser Engineering** (Nashville, Tennessee).

Effective May 1, 2009, the agreements are available to acute care and continuum of care members of the Premier healthcare alliance.

Premier also reported new agreements for hand-carried ultrasound have been awarded to **Sonosite** (Bothell, Washington) and **Terason Ultrasound** (Burlington, Massachusetts). Effective April 1, 2009, the 36-month agreements are available to acute care and continuum of care members of the Premier healthcare alliance.

- **Analytix On Demand** (Austin, Texas) and **Pervasive Software** (Irvine, California) are joining forces to deliver a business intelligence solution for the healthcare industry. Designed expressly for healthcare providers, large physician groups, hospitals, health plans and other healthcare organizations, the solution will provide a comprehensive, real-time view of business performance across clinical, financial and operational aspects of healthcare management. ■

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*Court report***Appeals court upholds most rulings in Boston Sci. vs. J&J****A Medical Device Daily Staff Report**

Sometimes when a court renders a decision it is difficult to tell the “winner” from the “loser,” especially where patent litigation is concerned. Case in point, a federal appeals court ruled Wednesday that **Boston Scientific** (Natick, Massachusetts) and **Johnson & Johnson** (J&J; New Brunswick, New Jersey) each infringed on each other’s patents in stent litigation that has been going on between the two companies for years.

According to the ruling, J&J’s Bx Velocity and Cypher stent systems infringe one of Boston Scientific’s patents,

but Boston Scientific’s Express, Taxus Express, and Liberté stents infringe one J&J patent while the Liberté stent infringes a second J&J patent.

The decision made by the Court of Appeals for the Federal Circuit mostly upheld a district court’s earlier decision. However, the court overturned one ruling against the Taxus Liberté stent. Damages will be determined in a future court proceeding.

“We are gratified the appeals court upheld the finding that the BX Velocity and Cypher stents infringe our patent and the patent is valid, and we are pleased the infringement claims against the Taxus Liberté stent were dismissed with prejudice,” said Jim Tobin, president/CEO of Boston Scientific. “We consider the outcome of this appeal to be highly positive.” ■

*New ventures***LHC to provide home nursing service in Alabama****A Medical Device Daily Staff Report**

LHC Group (Lafayette, Louisiana), a provider of home nursing services, reported that it has entered into a home health joint venture with **North Mississippi Medical Center - Hamilton** (Hamilton, Alabama), an affiliate of **North Mississippi Health Services**, to provide home nursing services in Hamilton, Alabama.

The primary service area of this joint venture spans six counties in Alabama, a Certificate of Need (CON) state. The estimated population of the service area is 200,000, with almost 16% over the age of 65. Net revenue for the Hamilton agency during the most recent 12 months was approximately \$900,000. This joint venture is not expected to add

materially to LHC Group’s earnings in 2009.

Keith Myers, CEO of LHC, said, “We are proud to be partnering with an organization with such an outstanding reputation and tradition of excellence as North Mississippi Health Services. Dan Wilford, one of our directors, used to serve as the CEO of North Mississippi Medical Center. As a result, we enter this new relationship knowing we have a strong partner that shares our commitment to quality care and efficiency. Together, our organizations will provide the residents of northwest Alabama with the highest quality of home care services.”

LHC also reported that it has entered into a hospice joint venture with 89-bed **Levi Hospital** (Hot Springs, Arkansas) to provide hospice services in central Arkansas. LHC Group and Levi Hospital have had a home health joint venture in place since December 2005. This hospice joint venture is not expected to add materially to LHC Group’s earnings in 2009. ■

ACC

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that those in the control group,” noted Dr. Alan Kadish, professor, Division of Cardiology, Feinberg School of Medicine, **Northwestern University** (Chicago). “We are particularly encouraged by the findings in this subgroup of patients and look forward to focusing on this subgroup in our next study.”

The Optimizer is CE marked and commercially available in Europe.

- **Atherotech** (Birmingham, Alabama), developer of the VAP Cholesterol Test, reported the addition of new cardiovascular and metabolic testing panels. Atherotech said it is adding more than a dozen new tests, including C-Reactive Protein (hsCRP), ApoE genotype, and NT-proBNP, for assessment of patients at intermediate to high risk of cardiometabolic diseases. The company is also adding advanced and follow-up cardiovascular disease (CVD) risk profiles.

“We’re maximizing the value of our core VAP technology with additional cardiometabolic tests,” said Atherotech President Michael Mullen. “This provides physicians and cardiology practices with a single source for the VAP Cholesterol Test plus the new test panels. You get the complete cardiovascular and metabolic view.”

The VAP Test, which recently added apoAI (and the apoB/apoAI ratio) to its panel, uses advanced lipid profile testing in the identification of individuals at increased risk of heart disease. The company said the new test panels enable Atherotech to increase its scientific and diagnostic capabilities by offering much more complete cardiometabolic testing.

The new test panels are available immediately and also include homocysteine, creatinine, creatine kinase (CK), HbA1c, TSH, ALT, AST, urea nitrogen (BUN), glucose, vitamin D, fibrinogen and insulin. The tests can be ordered individually, or bundled as part of a custom risk profile that may also include the VAP Test. ■

Pancreas

Continued from Page 1

OmniPod insulin pump and Personal Diabetes Manager that controls it – and a continuous glucose monitor, in this case either the FreeStyle Navigator from **Abbott Diabetes Care** (Alameda, California) or the DexCom STS7 from **DexCom** (San Diego). The new system includes an algorithm that automates the interaction between the pump and monitor, and facilitates the running of a variety of tests and challenges to the software and component devices. The UC Santa Barbara-developed software and algorithms are also being used with a number of other pumps and monitors in developing additional systems, according to the researchers.

Howard Zisser, MD, director of clinical research and diabetes technology at the Sansum Diabetes Research Institute, told *Medical Device Daily* that the new system provides a testing platform where researchers can test all of the components together, as opposed to testing each component individually. Hopefully, he said, that will help with the regulatory process of the artificial pancreas.

"I think it's nice for [FDA] to see everything operating as one . . . it really helps to have everything in one system that we can test the whole system," Zisser said. "You don't want to have a system that the components work but when you plug them all together they don't work and that is one of the concerns of the FDA . . . what happens when they start communicating together?"

The research is part of the artificial pancreas project, which is funded by the **Juvenile Diabetes Research Foundation** (New York) and is being conducted by an international group of diabetes research centers. The project's first goal is to integrate an insulin pump and continuous blood glucose monitor to closely replicate a healthy pancreas for patients with Type I diabetes – patients whose pancreases no longer produce insulin, which is used by the body to control blood glucose levels. An artificial pancreas will allow for tighter and automated control of blood glucose levels, which would significantly help to avoid the long-term complications of the disease.

"While we still have a ways to go, this new system brings us much closer to making the artificial pancreas a reality for Type I diabetes patients," said lead author Eyal Dassau, PhD, diabetes team research manager at UC Santa Barbara. "This achievement is vital – we now have a way, prior to patient trials, to fully verify and validate that an artificial pancreas can efficiently operate in the variety of conditions reflective of a large group of patients with this disease."

Zisser said the new system would help streamline the preclinical trials. "We plan to begin using it in the next several months," he added.

The other advantage of using the new system is that it is "plug and play," Zisser said. "We're going to be adding more pumps, more sensors, as they come on line." ■

Deals

Continued from Page 2

2009).

The transaction is expected to generate cash proceeds of \$275 million from the sale of property and equipment. From these proceeds, \$30 million will be deferred and placed in an escrow account for up to four years. In addition, Tenet's subsidiaries will retain substantially all of the hospitals' working capital, which is expected to result in about \$35 million of incremental cash proceeds. Tenet said it expects to use the proceeds for general corporate purposes.

USC has committed to offer employment to all or substantially all current employees who are in good standing. The transaction is subject to conditions and regulatory approvals that must be satisfied prior to closing. The closing, which is not conditional on financing, is targeted for completion by March 31. As part of the transaction, Tenet and USC will drop all litigation pending between them.

Tenet said it expects to record an impairment charge of about \$40 million, pre-tax and after-tax, in discontinued operations in 4Q08 related to the sale.

Tenet owns and operates acute-care hospitals and related ancillary healthcare businesses, which include ambulatory surgery centers and diagnostic imaging centers. ■

PEOPLE IN PLACES

• **Small Bone Innovations** (SBI; New York) reported changes to senior management. Steve Ward, in addition to being the company's CFO since March 2006, has been promoted to COO. SBI also reported that it has formed an Executive Management Committee, which consists of Anthony Viscogliosi (CEO/chairman), Thomas Crowley (president), Florian Kemmerich (president, SBI International) and Steve Ward (CFO/COO). Additionally, SBI has formed an Operating Committee to manage the day-to-day operating activities of the company. The Operating Committee is led by Steve Ward and also includes Thomas Loring (Senior VP Worldwide Product & Technology Development), James Hook (Senior VP, North American Sales), Jean-Jacques Martin (Senior VP, SBI International), Scott Ludecker (VP, Worldwide Diabetes and Limb Preservation Systems) and James O'Connor (VP, Worldwide Regulatory, Quality and Clinical Affairs, Surgeons Ethics & Compliance). Small Bone Innovations was founded in 2004 by Viscogliosi Brothers, a New York-based merchant banking firm that specializes in the musculoskeletal/orthopedic sector.

Magnetism

Continued from Page 1

They have developed a microfluidic system as a type of artificial spleen to battle the devastating effects of sepsis, a condition in which the bloodstream carries pathogens throughout the body to launch a wide-ranging inflammatory attack. Those that can't withstand this sort of systemic attack are most often newborns, the elderly and those that have already compromised immunity.

And the current therapies for these attacks – most often necessary in the intensive care unit – though multiple, are often insufficient for beating off the change from serious to massive infection.

The result: more than 200,000 die of sepsis infection every year in the U.S.

Rather than simply trying to kill the sepsis pathogens with antibiotic drugs, Ingber and his collaborators are developing a second line of defense – a microfluidic system for removing the patient's blood, using magnetism to pull out the threatening pathogens and then returning the cleansed blood to the body.

Key to this system, Ingber told *Medical Device Daily*, is a “counter-intuitive” property of the small channels of microfluidic systems, enabling two streams of liquid to be in side-by-side contact but still remaining separate.

One of those streams in the device developed by the researchers is the blood removed from the body. They then add tiny magnetic beads, pre-coated with antibodies which attach to specific pathogens that may inhabit the blood.

The second stream sent through the device is a saline-based “collection” fluid which runs beside the blood. As the two streams flow in the device, a magnetic field is then used to pull the magnetized bead/pathogen clumps out of the blood and into the collection fluid.

That fluid is then thrown away, the cleansed blood returned to the patient.

Explaining the counter-intuitive process behind this procedure, Ingber reminds the *MDD* reporter of some basic physics — specifically how, for instance, when two tributaries of streams or rivers merge, they mix, that mixture resulting in turbulence, an effect unwanted in the researchers' anti-sepsis device.

Instead, the small channels which are the primary features of microfluidic devices enable the two streams to be in contact but remain “laminar,” Ingber said, that is, continuing on without mixing or becoming turbulent.

This is the counter-intuitive and all-important characteristic of the system, he said, since any “compromising” of the blood – by clotting or loss of blood cells or any other change in its composition – would render the cleansing process ineffective.

Another key problem, he noted, is to avoid too strong a magnetic pull.

That too, he said, would result in turbulence in the flow of liquids as the result of “a big pile of beads forming in the

flow path, and clogging the vessel.”

“The trick is to produce an unlimited capacity for clearance,” Ingber said. “You don't want to compromise the blood in any way.”

The researchers report that a device with four parallel collection modules achieved more than 80% clearance of fungi from contaminated samples of blood in a single pass, at a flow rate and separation efficiency that would be viable for clinical applications.

And Ingber and his collaborators estimate that a scaled-up system with hundreds of channels could totally cleanse the blood of an infant within several hours.

“This blood-cleansing microdevice offers a potentially new weapon to fight pathogens in septic infants and adults . . . by removing the source of the infection and thereby enhancing the patient's response to existing antibiotics,” Ingber said, thus highlighting the device's usefulness in conjunction with antibiotic therapy.

The next step in the research, he said, is to test the device in rabbits, not just laboratory blood — rabbits essentially offer close to the same blood volume as a newborn – while also developing various device designs.

Ultimately, he envisions the system developed as a cassette that could be easily utilized with the current types of devices used to isolate and filter small chemicals from blood.

Currently, the researchers are binding magnetic beads with one type of molecule, but other more generic types of molecules could be used in the future for broad-spectrum cleansing, or using “multiple types of beads all at once, or molecules that bind many different pathogens.”

Ingber said it is difficult to judge when the system might reach clinical practice. But he indicated that if the team's animal research is able to demonstrate efficacy, “it could have a significant impact in saving lives.”

As to winning FDA regulatory approval, he added: “Given the life-threatening situation [offered by sepsis], it might be sooner than later.”

The researchers at Children's Hospital Boston and collaborators from Draper Laboratories were funded by a grant from the **Center for Integration of Medicine and Innovative Technology** (CIMIT; Boston); they also recently won a \$500,000 grant from CIMIT to advance this work. ■

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Stryker

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tein (BMP) variant known as BMP-7 and a collagen derived from bovine sources. OP-1 Putty differentiates partly due to the addition of carboxymethylcellulose to the mix.

According to company documents, the putty product has been used on more than 15,000 patients in the U.S. and another 25,000 in other nations with “no specific safety trends observed.” The pivotal trial compared OP-1 Putty to the use of bone graft harvested from the crest of the hip-bone to fuse lumbar vertebrae for patients with degenerative spondylolisthesis who have not responded to six months of conservative therapy. The idea behind the product is to eliminate the need to harvest bone from the hip, a procedure described as painful and requiring longer procedures and more hemorrhage. The original plan was to follow the patients for 24 months using conventional X-ray scans to evaluate whether the vertebrae have fused.

The first analysis of the completed trial data showed that the OP-1 performed better than bone graft in terms of neurological success and the need for re-operation. However, patients in the control arm (bone graft) scored better on the presence of new bone by X-ray and on scores of the Oswestry disability index, a now-commonly used index of patient mobility. Thus the trial failed to demonstrate non-inferiority of the OP-1 to graft.

One of the problems encountered in the first analysis of the pivotal trial was that the Putty tended to migrate from the original point of placement, and the location of bone growth was consequently not where clinical investigators anticipated, leading to questions about the amount of regrown bone. This was the impetus behind the use of CT scans to re-evaluate the patients at 36 months. However, the company also expanded the margin for non-inferiority from 10% to 14% on scans at the same time, generating a new set of conditions for FDA to consider and the panel to consider. The number of fatalities in the study arm was 11, compared to five in the control group, but the rate of death was lower for the study subjects due to enrollment of 208 in the study arm and only 87 in the control arm.

Eugene Poggio, PhD, a consulting biostatistician, noted the original protocol’s requirement of a non-inferiority margin of 10% and that the first analysis of the trial showed an overall success rate at 24 months of 38.7% for OP-1, and 49.4% for autograft. He said, “our intent in designing the extension study was to use the same primary endpoint,” and get all the original patients back in. “Approximately 80% of eligibles participated in the extension study,” he said, adding that the extension analysis led the firm to conclude that “OP-1 is at worst 11.6% worse than autograft and at best, 12% better than autograft.”

Poggio also argued that the sensitivity analysis indicated that “the two treatments are virtually identical in overall success rates,” and that “the two treatments are very similar, regardless of how you handle the missing

data,” a reference to the fact that not all the original patients participated in the extension study.

Jianxiong Chu, PhD, a biostatistician with the agency, told the panel, “the sponsor’s proposal to allow a larger non-inferiority margin [in the extension study] is not justified from my statistical point of view.” Chu remarked that FDA has “issues with such a post-hoc analysis,” adding that “the sponsor’s [modified intent-to-treat] analysis . . . still fails to support the non-inferiority claim.”

Another issue that cropped up was whether the device would spur immunological reactions that would create adverse events, a concern that seemingly was unmollified by the extensive data behind the device. This concern revolved around the possibility that the sterilization of OP-1 with irradiation would carry a toxic effect.

Also presenting on the company’s behalf, David Wong, a former president of the **North American Spine Society** (Burr Ridge, Illinois), said the use of conventional X-rays is “an unreliable way to determine whether there is a solid bridge” between the vertebrae. Another spokesman for the company said that the data demonstrated “no difference in terms of biomechanical stability.”

When it came time for the vote, panelist Brent Blumenstein, PhD, of **Trial Architecture Consulting** (Washington) moved for non-approvability, stating “I am unconvinced that the data provide sufficient evidence of efficacy.” Janine Mason, MD, of **Jason and Jarvis Associates** (Hilton Head, South Carolina) commented, “I think that the data is really not quite adequate” regarding immunological safety and opined that a new study would be needed to establish this.

Raj Rao, MD, of the **Medical College of Wisconsin** (Milwaukee), remarked that he voted for disapprovability because of a “lack of clear radiographic superiority.” He said he had “no major concerns with regard to safety issues, but some concerns about . . . fetal maldevelopment down the road.”

Panelist John Kirkpatrick, MD, of the **University of Florida College of Medicine** (Jacksonville), commented that he was “concerned about the post-hoc analysis that had to be done to yield a positive result” and whether “fusion happens, even when there’s bone there.” Surgeons typically abrade the vertebrae in the fusion site to trigger bone growth, and some panelists indicated that they felt this could account for some of the effect seen in the study arm patients. Kirkpatrick also said “I still have the concern over the very rare instance” of a potentially “catastrophic event.” ■

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Implants

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cochlear implant expert Hugh McDermott, PhD, professor of auditory communication and signal processing in the Department of Otolaryngology, **University of Melbourne** (Australia), told *Medical Device Daily*. "They work quite well for people listening to speech when it's quiet and if there's not much background noise. But the ability of the person to understand speech in a noisy place, like a restaurant, is difficult.

"The other problem is pitch perception, which is important for following music and for people who speak tonal languages such as Cantonese and Mandarin because they contain tones that equate meaning. Cochlear implants are poor about giving information about the pitch," said McDermott, who is also a senior member of **IEEE** (Washington), a professional association for the advancement of technology.

The clarity and usefulness of these little devices boils down to the number of electrodes that can be used in an implant. Most implants have up to 24 electrodes. But they are intended to make up for the estimated 16,000 delicate hair cells that are part of a normal hearing ear. Cost, too, is another obstacle. Most implants average \$60,000 including surgery and hardware, according to the NIDCD.

Also known as bionic ears, these devices aren't just souped-up hearing aids, which amplify sound. Instead, they stimulate functioning auditory nerves inside the cochlea with an electric field. The connected external components include a microphone and speech processor.

McDermott, whose research centers on the development of cochlear implants and advanced hearing aids, invented the widely used speech-processing strategies known as SPEAK and ACE. (Cochlear implants are capable of delivering stimulation in several different ways, each of which is called a speech strategy.)

Most implants on the market today are made by just a few companies, with one that dominates, according to McDermott: **Cochlear** (Melbourne, Australia) makes the Nucleus Cochlear Implant System, which was FDA approved in 1998, now a fourth-generation version.

The number of devices implanted in humans varies, according to the source, from 112,000 up to 170,000. But that's still a drop in the bucket compared to the millions of people who could potentially benefit.

Other implant makers include:

- **Advanced Bionics** (Sylmar, California) received FDA approval to market the Clarion Multi-Strategy Cochlear Implant in 1997.

- **Med-El** (Research Triangle Park, North Carolina) makes the FDA-approved Combi 40+ Cochlear Implant System.

- **Symphonix Devices** (San Jose, California) makes the Vibrant Soundbridge, FDA approved in 2000. At the time, the agency called it the first implantable hearing device approved in the U.S. to treat moderate to severe sensorineural hearing loss – the result of hair cells, or nerves in the inner ear, being damaged. This type of hearing loss

affects the vast majority of people with hearing loss.

"These products are all quite similar on a basic level," McDermott said. "They all have an external device that looks like a hearing aid and it extracts information about sounds and transmits through the skin to the implant, which picks up the signal and generates pulses that are delivered to the inner ear. The cochlear sound is converted into neural activity."

Two other companies have been working on technology that compares to the Symphonix implant, including **Implex** (Ismaning, Germany) and **Otologics** (Boulder, Colorado).

In addition to technological challenges faced by these implant makers, they have been faced with other difficulties. For instance, the FDA reached a settlement with Advanced Bionics over alleged violations involving the failure to notify the agency of a change of outside supplier or vendor, which may have exposed patients to unnecessary health risks, such as device failure and surgery, according to the FDA (*MDD*, July 18, 2008). The company had to pay a penalty of \$1.1 million. In March 2006, Advanced Bionics conducted a recall of the unimplanted devices containing components from the unapproved supplier, because of excessive moisture that could leak into the devices and cause device failure and possible surgery.

Last year, the FDA sent a warning letter to Cochlear's Swedish subsidiary (Molnlycke, Sweden) with citations related to deviations from good manufacturing practices (*MDD*, Aug. 27, 2008).

Then, a study published just two years ago confirmed what many physicians have frequently speculated, that the presence of cochlear implants increases the risk of bacterial infections that can cause meningitis (*MDD*, April 12, 2007). The report, which appeared in *Otolaryngology-Head and Neck Surgery* said that the finding increases the need to educate the public on the necessity for meningitis vaccinations in potential cochlear implant recipients. At the time, 90 of the 60,000 people receiving cochlear implants were stricken with meningitis, drawing concern within the international medical community.

So what's on the horizon in terms of improved devices, possibly one that's completely implanted yet with better clarity?

"There is a bit of controversy about totally implanted devices," McDermott said. "A lot of people would like to have a totally implanted device, giving them ability to hear 24 hours a day and when swimming or showering because the external component can't get wet. One of the controversies is that some people with hearing impairment prefer that it's partially visible because they want people to know they have a hearing impairment because cochlear implants and hearing aids don't restore normal hearing. So if you're in a noisy situation it might be helpful for the person to know you have a hearing impairment to speak clearly and directly."

He explained that with current technology, there would be a trade-off with a totally implanted version.

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PRODUCT BRIEFS

- **ContextVision** (Stockholm, Sweden) has introduced the GOPICE US, a real-time volumetric filtering software for ultrasound. The image enhancement product filters the three-dimensional ultrasound volumes, removing speckle and other artifacts, while simultaneously extends the clinician's vision to planes previously hidden. Like all ContextVision products, GOPICE US relies on an adaptive algorithm, GOP, which mimics the human eye's method of finding information and analyzing structures. This enables the software to distinguish between true and false information (e.g. noise, artifacts) and accurately identify true structures.

- **DePuy Spine** (Raynham, Massachusetts) said it has begun testing of a genetically engineered human protein in patients with moderate to severe low back pain. The first in a series of clinical studies evaluating the safety and effectiveness of the protein, intradiscal rhGDF-5 (recombinant human growth and differentiation factor-5), began at **Texas Back Institute** (Plano). The study outcomes will evaluate if injections of rhGDF-5 into the lower spine can relieve pain and slow or even reverse early stage degenerative disc disease. The study consists of patients who have had persistent discogenic back pain for at least three months at one symptomatic lumbar level from L3/L4 to L5/S1 and who have not responded to conservative medical treatment such as physical therapy. Clinical outcomes will be measured using standard validated tools and lumbar disc changes will be measured using magnetic resonance imaging data.

- **Invitrogen** (Carlsbad, California) reported the launch of the GIBCO OptiCHO Protein Express Kit, an integrated solution for development of serum-free, stable cell lines for biotherapeutic development. This kit provides cells banked under cGMP conditions, enabling biotherapeutics manufacturers to speed regulatory submissions and time to market. The GIBCO OptiCHO Protein Express Kit enables biotherapeutics manufacturers to develop stable cell lines where proteins of therapeutic interest can be expressed and reproduced. It uses all of the reagents, pro-

MOBILITY trial begins for Absolute Pro stent system

A Medical Device Daily Staff Report

Abbott Laboratories (Abbott Park, Illinois) reported the initiation of MOBILITY, a clinical trial studying the safety and efficacy of the Absolute Pro peripheral self-expanding stent system in patients with iliac artery disease. Iliac artery disease is a form of peripheral artery disease (PAD) that affects the lower extremities.

The Absolute stent is a self-expanding nitinol stent with a flexible and conformable design that is intended to keep lesions open without introducing more metal than necessary to treat a narrowing. The peripheral stent delivery system is compatible with 0.035" (0.89 mm) guide wires.

The primary endpoint of the MOBILITY trial is a composite measure of major adverse events (MAE) at nine months. MAE is defined as death due to any cause, heart attack (myocardial infarction), clinically driven target lesion revascularization and limb loss (amputation only) on the treated side(s).

Abbott's vascular research program includes clinical trials in peripheral artery disease, carotid artery disease, and coronary artery disease.

protocols and documentation required to go from gene to stable cell clones expressing the protein of interest within a completely serum-free process. All of the products within the workflow are animal-origin free, which supports bio-manufacturers' ability to enhance the safety of human therapeutics.

- **Medtronic** (Minneapolis) began the international launch of the Driver Sprint RX Coronary Stent System, which received the CE Mark in February 2009 and is planned to be commercially available in more than 100 countries worldwide. The new system incorporates a new tip design for a low profile and an enhanced shaft design which together greatly improve the device's deliverability. These innovations are also incorporated in Medtronic's Endeavor Sprint and Resolute Drug-Eluting Stent Systems.

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"You get the benefit [of a device that's totally implanted], but you lose performance. As soon as you implant a microphone under the skin, the ability to pick up sound is lost and the internal noises increase, such as breathing, chewing and other body noises," McDermott said. "It's why totally implanted devices haven't moved ahead of the experimental stage."

Better devices, he said, come down to the number of electrodes and will require radical rethinking.

"The problem is that we don't understand enough about

how normal hearing works," he said. "We're trying to emulate a natural process that people don't really understand. It's also possible that it will never work. When you use electrical stimulation in the cochlea with an impairment, it's not normal. The auditory nerve may be too small or damaged to give good information. If that's the case, there's a completely different line of research on the way to make the neurons grow or to help existing neurons to survive."

Further down the line, McDermott says the real answer may be found in gene or stem cell therapy.

"Forget about implants, this approach would have cells inside the cochlear regrow for those that are damaged or