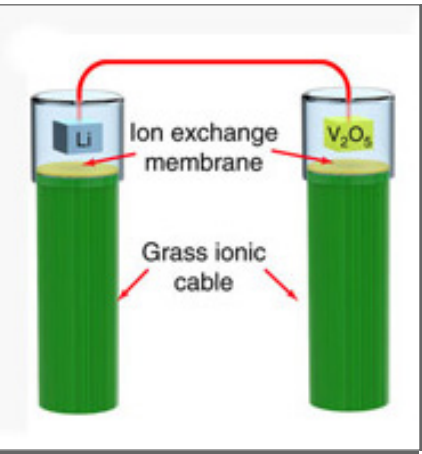
BioWorld MedTech

Clarivate Analytics

The news source of record covering the latest advances in medical technology
Actionable Intelligence • Incisive Analysis

July 27, 2017
Volume 25, No. 144



Bid for biocompatibility

Engineers design first ionic current battery using natural materials

By Stacy Lawrence, Staff Writer

The human body uses a different form of energy than electrical currents generated by a typical battery. But now, for the first time, University of Maryland engineers have developed a battery that generates ionic currents, which is how electricity is created in the body and all living organisms.

The expectation is that this could lead to a biocompatible battery for use in brain and muscle-

See Ionic battery, page 3

Inside

Throwback device moving back to the forefront

Trina Health, Animo's 'pump' shown to be effective at mimicking pancreatic function

By Omar Ford, Staff Writer

A device developed more than two decades ago could finally be used as an effective treatment in diabetes. Trina Health Midwest LLC's Bionica microdose pump was demonstrated to "closely

See Animo, page 4

Regulatory

EU parallel review en route via EMA, EUnetHTA accord

By Mark McCarty, Regulatory Editor

Device makers have rarely availed themselves of parallel FDA-CMS review of their devices, but drug and device makers doing business in the European Union may soon be able to invoke a similar mechanism thanks to an agreement

See EU, page 6

Cambridge tests breath biopsy

Owlstone joins Cancer Research UK in breath-taking hunt for cancer biomarkers

By John Brosky, Contributing Writer

PARIS – Breaking with the established wisdom for start up companies to sharply focus on executing a single mission, London-based Owlstone Medical Ltd. is launching a scatter gun strategy

See Owlstone, page 8

Less pain at injection

Milestone Scientific receives FDA nod for Compuflo epidural device, appoints new CEO

By Katie Pfaff, Staff Writer

Milestone Scientific Inc. won FDA marketing clearance for its Compuflo epidural instrument to provide more precise injection and reduce pain. Daniel Goldberger was tapped as CEO to lead the

See Milestone Scientific, page 5

Genome therapy promises new blood disease treatments

By John Fox, Staff Writer

HONG KONG – In a study led by Australian scientists at University of New South Wales (UNSW), introducing a beneficial natural mutation into blood cells using gene-editing was shown to stimulate production of fetal hemoglobin (Hb), a finding that could lead to a cure for blood diseases.

People with potentially life-threatening blood disorders, such as thalassemia or sickle cell anemia (SCA), have impaired adult Hb, so they require life-long treatment with blood transfusions and medications.

However, available treatments are limited regarding efficacy, tolerability and cost. "A number

See Science, page 7

BioWorld Medtech's Orthopedics Extra

Executive Editor Holland Johnson on one of med-tech's key sectors

Read this week's edition

Appointments and advancements

Adaptive Biotechnologies Inc., of Seattle, reported the appointment of Gene DeFelice to senior vice president and general counsel, and Alexandra Snyder to Translational Medicine Lead for Adaptive Research.

Nemaura Medical Inc., a Loughborough, U.K.-based company focused on the development and commercialization of Sugarbeat, a wireless disposable adhesive skin-patch for adjunctive use by diabetics as a noninvasive and needle-free continuous glucose monitoring system, has appointed Salim Natha to the company's board. Natha will serve as an independent director of the company and chair the board's compensation committee.

Tenet Diagnostics Inc., of Kenilworth, N.J., reported the appointment of Scott Howell as chief medical officer. Howell brings managed care experience with health plans, most recently as executive medical director at Heritage Provider Network, a fully delegated medical group.

Daily M&A

Cas Medical Systems Inc. (Casmed), of Branford, Conn., reported the sale of its noninvasive blood pressure monitoring product line, including Maxnibp and Maxiq technology, for $4.5 million in cash to **Suntech Medical Inc.**, a Morrisville, N.C.-based subsidiary of Halma plc. Casmed will be eligible to receive up to an additional $2 million in cash based on the achievement of certain sales criteria through June 2019. The company will provide transition services as necessary. Suntech will also purchase the related product inventory at the end of that short transition period.

Cogentix Medical Inc., Minnetonka, Minn.-based provider of urology and gynecology devices, acquired privately held **Genesis Medical Ltd.** based in London. The transaction is expected to generate incremental revenue to Cogentix during the second half of 2017 of approximately $0.8 million and more than $2 million of incremental revenue in 2018. Genesis sells and markets a variety of products to urologists within the U.K. and has been the exclusive U.K. distributor of Cogentix's Primesight endoscopy systems since 2013. Under the terms of the acquisition agreement, Cogentix has purchased the tangible assets of Genesis and will pay up to £515,000 (US$672,105) for the ongoing business, dependent on Genesis achieving certain revenue milestones through March of 2019.

Other news to note

Accenture, of Arlington, Va., will collaborate with Switzerland-based **Roche** to improve diabetes management by bringing its data analytics platform to Roche's digital diabetes offerings. Accenture's platform and Roche's portfolio will connect patients, caregivers and healthcare providers with a suite of digital health services.

Reston, Va.-based **Avizia** will partner with **Ascom**, of Raleigh, N.C., to integrate Avizia's secure provider messaging application with Ascom's Myco smartphone for health care providers.

Alameda, Calif.-based **Biotime Inc**. shared the Data Safety Monitoring Board has authorized the company to begin enrolling cohort 3 in its phase I/IIa Opregen clinical trial, which addresses the dry form of age-related macular degeneration with intraocular injection of suspended Retinal Pigment Epithelial cells. The cohort will include patients at sites in Israel and the U.S.

Lexington, Mass.-based **GI Dynamics Inc.**, maker of Endobarrier for patients with type 2 diabetes and obesity, chose **Proven Process Medical Devices Inc.**, of Mansfield, Mass., as contract manufacturing partner. The latter will begin manufacturing the device at its facilities.

BioWorld MedTech

BioWorld MedTech (ISSN# 1541-0617) is published every business day by Clarivate Analytics.

Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement.

Our newsroom

Lynn Yoffee (News Director), Holland Johnson (Executive Editor), Mark McCarty (Regulatory Editor), Andrea Gonzalez (Production Editor)

Staff writers: Omar Ford, Katie Pfaff, Bernard Banga, John Brosky, David Godkin, Larry Haimovitch, Stacy Lawrence, Alfred Romann, Tamra Sami

Business office

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

Contact us

newsdesk@medicaldevicedaily.com

Donald R. Johnston, (770) 810-3118 // Holland Johnson, (770) 810-3122 // Omar Ford, (770) 810-3125 // Mark McCarty, (703) 966-3694 // Andrea Gonzalez, (770) 810-3049 // Penney Holland, (770) 810-3047 // Lynn Yoffee, (770) 810-3123

Practical information

For Sales Inquiries: http://clarivate.com/life-sciences/news/bioworld/#. NORTH AMERICA, Tel: +1-855-260-5607. Outside of the U.S. and Canada, Tel. +44-203-684-1797. For Customer Service Inquiries, NORTH AMERICA, Tel: +1-800-336-4474. Outside of the U.S. and Canada, Tel. +44-203-684-1796.

For ad rates & information, contact Chris Venezia toll free at (855) 260-5607 or, outside the U.S. and Canada, at (646) 522-6243, email christopher.venezia@clarivate.com.

For photocopy rights or reprints, please contact Chris Venezia toll free at (855) 260-5607 or, outside the U.S. and Canada, at (646) 522-6243, or by email at christopher.venezia@clarivate.com.

Send all press releases and related information to newsdesk@medicaldevicedaily.com.

Ionic battery

Continued from page 1

stimulating medical devices; it could even form the basis for bioelectronics, miniaturized low-power implants that are expected to stimulate the body to treat a wide range of diseases.

Their results, using blades of Kentucky bluegrass in lithium salt solution to store and conduct the energy to stimulate living cells in a petri dish, were published in the July 26 issue of *Nature Communications*. A proof-of-concept experiment applied the battery, known as an electron battery, to stimulate a single layer of cultured cells that fluoresce when stimulated with a controlled ionic current.

"We are developing a smaller device and cables to use for a specific application. That application could be to stimulate muscles or to treat bipolar disorder," lead author Chengwei Wang, a graduate student in the materials science and engineering department at the University of Maryland in College Park, told *BioWorld MedTech*.

He added that his group plans to work with cross-disciplinary research groups to select initial biomedical applications.

"First, we need to find real applications for a specific disease; we need to pick out the mechanism to find out how this really works in a biosystem." Wang continued, "We can design our device either smaller or to generate specific ions for specific applications. We can also upsize our device to meet requirements for specific applications." Optimizing and miniaturizing the cable for conduction is also a priority.

A typical battery delivers electrical energy in the form of moving electrons; this is generated by moving positive ions from one end of the battery to the other. The new battery does the opposite by moving electrons around the device to delivery energy out as a flow of ions.

Grass fibers were used as the basis for both energy storage and as the cable for connectivity. The initial construction of the battery itself was of two glass tubes, each with a blade of grass inside and connected by a thin wire on top to move electrons back and forth. At the other end of each tube is a metal tip out of which ionic current flowed. In addition to the fluorescing petri dish proof-of-concept, the researchers were able to move dyed blue copper ions along a lithium-soaked cotton string.

The engineers expect to be able to tailor the electrode materials and ionic cables by soaking them with various ions, including an ion flow of lithium, sodium, potassium and calcium. All of these are involved in various bodily biological processes. This could be used to change concentrations and charges of the cell membrane, thereby modulating cellular behavior. The electron battery is expected to be able to interact with cells at any current level.

Budding bioelectronics

"An initial application could be very soon. In bipolar disorders, patients are taking lithium. That salt can affect your nervous system. Say the battery is a lithium, small device – an implant put in your brain that can generate and release lithium in a small area to affect disease. The impact throughout the body will be much smaller than taking lithium, with no side effects," explained Wang.

In the longer term, this new technology could serve as a means to interact even more intimately and elaborately with the nervous system. Wang speculated that the technology could serve as a means to subtly, but effectively, hack directly into the human body.

> *"This battery . . . could be like a PC in the body. It could communicate with the nervous system like you program a computer.*
>
> Chengwei Wang
> Graduate student, the University of Maryland

"Think about it like a computer, that's very powerful. This battery could directly interact with the body; it could be like a PC in the body. It could communicate with the nervous system like you program a computer. The potential for applications could be great, but it depends on how you solve the puzzle. You need researchers from different backgrounds," he said.

Added Jianhua Zhang, a staff scientist at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that is part of the National Institutes of Health (NIH) in Bethesda, Md., who conducted the cellular experiments, "The battery could be used to develop medical devices for the disabled, or for more efficient drug and gene delivery tools in both research and clinical settings, as a way to more precisely treat cancers and other medical diseases. Looking far ahead on the scientific horizon, one also hopes that this invention may help to establish the possibility of direct machine and human communication."

He cited Alzhiemer's disease and depression as potential indications that could benefit from next-gen devices that can micro-manipulate neuronal activity and interaction.

Bioelectronics, a field that aims to manipulate the chemical makeup of the body in order to treat disease via tiny device implants, seems a natural fit for applications of this novel electron battery. Ambitious efforts on this front got a boost with the creation last August of joint venture Galvani Bioelectronics Ltd. by Glaxosmithkline, which has long supported bioelectronics research, and Verily Life Sciences LLC, a subsidiary of Google parent Alphabet Inc. They have committed investing more than $700 million over seven years. (See *BioWorld MedTech*, Aug. 2, 2016.)

The researchers on the electron battery are working with multiple potential ionic conductors including cellulose, hydrogels and polymers. The grass used in this experiment holds the salt solution, making it a stable ionic conductor. The research team has previously studied using cellulose and plant materials to create a battery.

"My intention is for ionic systems to interface with human systems," said Liangbing Hu, the head of the group that developed that battery and a professor of materials science at the University of Maryland. "So, I came up with the reverse design of a battery. In a typical battery, electrons flow through wires to interface electronics, and ions flow through the battery separator. In our reverse design, a traditional battery is electronically shorted (that means electrons are flowing through the metal wires). Then ions have to flow through the outside ionic cables. In this case, the ions in the ionic cable – here, grass fibers – can interface with living systems." ♦

Animo

Continued from page 1

replicate" normal pancreatic function, results from a study published in the July edition of *The Journal of Diabetes, Metabolic Disorders & Control* show.

The study, titled "Microburst insulin infusion: results of observational studies – carbohydrate metabolism, painful diabetic neuropathy, and hospital/emergency department utilization," looked at more than 2,000 patients.

The Bionica microdose pump uses IV infusion to mimic the insulin pulses of a healthy pancreas in what the company calls the Artificial pancreas treatment (APT). This in turn stimulates the liver to produce the enzymes necessary for carbohydrate metabolism, which lowers lipid metabolism, resulting in more cellular energy in body tissues.

The process is monitored by frequent glucose levels and metabolic measurements. APT is done over one-hour periods with a rest period between each session for three courses each day of treatment. Typically, APT is performed on a weekly or bi-weekly basis following the first week of two back-to-back daily sessions.

To commercialize the device, which is a little larger than a smartphone, San Diego-based, Trina Health began a partnership with San Clemente, Calif.-based Animo Health Inc., late last year.

"The device was still in use, but it just wasn't commercialized enough to the point where it would start helping people en masse," Mark Pound, president and CEO of Animo Health, told *BioWorld MedTech*.

He stressed the device is not a cure for diabetes.

Study results

The study published in *The Journal of Diabetes, Metabolic Disorders & Control* is based on data from three observational retrospective studies that underscore the effectiveness of microburst insulin infusion.

The carbohydrate metabolism portion of the study suggests APT has a dramatic effect on carbohydrate metabolism; this is of particular importance as the inability to properly metabolize carbohydrates represents a core dysfunction in diabetes.

In the painful diabetic neuropathy portion of the study, among the 412 patients studied over a three month period, APT completely eliminated or significantly reduced pain in 93 percent of the patients.

Finally, in the two-year restrospective hospital and emergency room validation portion of the study, which evaluated 1,524 patients, it was shown that APT significantly reduced the number of hospital and emergency visits. According to Matched National Hospital Discharge Survey and U.S. Agency for Healthcare Statistics, expected hospitalization rate is 94 per 1,000 patients over a two-year period and the study showed the APT rate was five. Expected emergency room visits are 116 per 1,000 patients over two years and the APT rate was seven.

"I think the study points out what we've known for a while and we put this together to prove it," Pound said.

Stepping out of the shadows to take on the competition

Trina Health was formed by Ford Gilbert after it was discovered

> *"He gave up his legal career and immersed himself in the medical world, specifically in the world of diabetes. It's really an amazing story.*
>
> Mark Pound
> President and CEO, Animo Health Inc.

his daughter suffered from type 1 diabetes in the early 1980s. Gilbert, who was once an attorney, enrolled in medical school, started a nonprofit research institute and eventually created the Bionica microdose pump. Gilbert's daughter received the first treatment from the device when she was 5-years-old. Now she is 34-years-old, and has given birth to five children.

"He gave up his legal career and immersed himself in the medical world, specifically in the world of diabetes," Pound said. "It's really an amazing story."

Bionica microdose pump; Trina Health Midwest LLC

Other products on the market

Other companies such as Dublin-based Medtronic plc and Germantown, Md.-based Senseonics Inc. have made waves with artificial pancreas applications.

Medtronic received FDA approval for its Minimed 670G hybrid closed loop system in September 2016, and launched the device in June. (See *BioWorld MedTech,* Sept. 30, 2016.)

"It's not apples to apples," Pound said when comparing Medronic's device and the APT therapy. "There is a difference. What Medtronic calls an artificial pancreas is really a closed-loop glucose monitoring system that is developed subcutaneously. Whereas we're actually an artificial pancreas treatment."

There could be tremendous opportunities for companies to compete with Medtronic's artificial pancreas, said Sean Lavin an analyst with BTIG.

"Of note, from the 700-patient training phase [of Minimed 670G], Medtronic disclosed 83 percent satisfaction with the device and 96 percent satisfaction with the training," Lavin said. "The device satisfaction is strong, but at 83 percent in a hand-picked group of patients indicates to us that the 670G will not be for everybody."

Senseonics could see an approval by the beginning of next year.

"We assume a panel and approval near year end, but it could come sooner if the FDA decides not to have a panel," Lavin said.

Pound said while the competition is much bigger and not much is known about Trina Health, the publication of the data could help bring awareness to the Bionica microdose pump.

"We've already started to see [an increased] interest in the technology," Pound said. ♦

Milestone Scientific

Continued from page 1

company to commercialize the device. Former CEO, Leonard Osser, will remain on the board and become director of China operations.

The Compuflo epidural computer controlled anesthesia system is designed to assist practitioners in finding the epidural space objectively, recording information about the pressure, and ultimately causing less pain for patients.

Using its Dynamic pressure sensing (DPS) technology, the epidural device provides anesthesiologists with indication of pressure at the needle tip in real-time so they can locate the epidural space with "objective" guidance. Anesthesiologists would otherwise determine the epidural space through subjective skills developed over time, such as feeling the difference in pressure while pressing the needle.

"The [Compuflo epidural instrument] can aid in identification of the epidural space and can record in real-time," Mark Hochman, Milestone's director of clinical affairs and director of R&D, told *BioWorld MedTech*. Standard epidural injections depend on loss of resistance, a subjective measurement said Hochman, and a method that is difficult for doctors to master. "Our device can objectively identify the epidural space," said Hochman.

The device system is made up of a 20 mL syringe, pressure transducer, tubing set, ID adaptor and console with integrated touchscreen. The anesthesiologist would attach a standard epidural needle to the system. With the DPS, doctors are alerted to pressure at the needle tip with differing audible chimes, and also can record the tissue pressure sensed with the device, for later use in analysis.

Pressure means pain

Pressure sensation in the syringe tip can be used to identify different tissue types.

"[With the device] doctors have the ability to target tissue type because of pressure," said Hochman. He explained the device also allows anesthesiologists to dispense from the syringe and control the pressure at the tip of the needle in real-time. An ability to control flow rate and pressure results in reduced pain perception, said Hochman, since that is tied to the pressure on tissue.

"[Compuflo] offers more precise injection, documentation and reduced pain perception," said Hochman. "Prior to this, an injection would only control flow rate. This allows for control of flow rate and pressure, so it reduces pain perception."

Epidural injections are used for pain in acute care such as for childbirth, but also musculoskeletal pain intervention with steroid injections. Epidural injection carries a risk of incorrect injection leading to punctured dura, infection, effects from incorrect placement, or associated risks with injected material.

Infection risk

According to a 2008 article, "Complications and pitfalls of lumbar interlaminar and transforaminal epidural injections," in *Current Reviews in Musculoskeletal Medicine,* infections occur in 1-2 percent of spinal injections and can include meningitis, epidural abscess, discitis and osteomyelitis. Staph was cited as the most common infection. Infection by "gram-negative anaerobes can theoretically occur by unintentional penetration into the intestinal or pelvic cavity," states the article. "The needle can unintentionally go through the dorsal foramen and past the ventral foramen entering the pelvic cavity," according to the article, which suggests the needle be guided by imaging this area of the body.

Compuflo epidural instrument; Milestone Scientific Inc.

> *"The [Compuflo epidural instrument] can aid in identification of the epidural space and can record in real-time.*
>
> Mark Hochman
> Director of Clinical Affairs and R&D, Milestone Scientific Inc.

Milestone also markets the Wand handpiece, a dental instrument designed to target a specific tooth for anesthesia. Formerly named STA single tooth anesthesia system, the Wand is a computer assisted anesthesia system that allows for more control for the dentist, leading to a more accurate placement and medication that takes effect more quickly.

The company is researching future applications for the device in subcutaneous injections. These could include intra-articular injections, dermal filler, neurosurgery, ophthalmologic surgery, and self- injections. Hochman shared the company was currently investigating the possibility of usage with botox injections to better guide injections and reduce pain. A CE mark has been obtained in Europe for epidural and intra-articular injections.

Appointment and outlook

Newly appointed CEO Goldberger will launch the device to the market and manage a transition "to a commercially focused global medical device company," according to the firm, identifying key opinion leaders and developing collaborations with distributors. He previously served on the board or held senior management roles at Xtant Medical Holdings, Sound Surgical Technologies/Solta Medical, Xcorporeal and Glucon.

Placement or positioning has been approached in several ways in the device market. Medical suppliers such as Universal Medical, of Walpole, Mass., and Meditek, of Canada, make epidural positioning devices that put the patient in an ideal position for injection. Bard Inc., of Salt Lake City, markets its Statlock epidural stabilization device that uses an adhesive pad that secures the catheter so that it does not dislodge. Rivanna Medical LLC, of Charlottesvile, Va., offers its Accuro device for quick epidural location and depth monitoring. The device images the area while epidural or spinal anesthesia is being delivered. ♦

EU

Continued from page 1

between the European Medicines Agency and the European Network for Health Technology Assessment.

The parallel review program between the FDA and the Centers for Medicare & Medicaid Services, first announced as a pilot program in 2010, has been successfully invoked on only one occasion, which led to the approval of and coverage for the Cologuard test by Exact Sciences Corp. of Madison, Wisc., in 2014. Another application might have come through but for the fact that phase III study data for the Symplicity renal denervation device missed the primary efficacy endpoint. Even if one assumes Medtronic of Dublin had managed to shepherd the Symplicity through the parallel review process, the fact that only two applications would have made the grade in the nearly seven years the program has been available suggests device makers are at the very least wary of financing a clinical trial that will address both the safety-and-efficacy and the reasonable-and-necessary evidentiary standards. Whether a similar reluctance will accompany the new EU parallel consultation program will not be in evidence for some time, however.

A statement posted at the website for the European Network for Health Technology Assessment (EUnetHTA) describes the program as an effort to provide sponsors "simultaneous, coordinated advice on their development plans," which should in turn "facilitate alignment of data requirements." This program will in some cases supplant a state-by-state effort between EMA and national health technology assessment agencies, but these state-based agencies will not necessarily be pushed out of the picture.

EUnetHTA said these parallel consultations would commence before pivotal trials are started, but as many as three national HTAs would be involved in the consolidated parallel consultation for an applicant product. Sponsors can still opt for a single-state parallel review as well. Despite the availability of a single-state parallel consultation, EUnetHTA will serve as "the sole contact point" for the national HTA agency in question.

The applicant company can request which national HTA agencies it would like to handle a consolidated consultation, although there are no guarantees that such requests will be fulfilled. Interestingly, the sponsor's choice of an HTA entity for an individual, nation-specific consultation is likewise not guaranteed.

The parallel consultation program will be updated over time, EUnetHTA said, with some updates relying on "the advent of sustainable funding mechanisms," which would presumably be provided by the EU. This program will not be available to any product, however, but instead will be limited to products that fulfill each of three requirements, including that the product invoke a new mode of action. The applicant must also demonstrate that their candidate drug or device targets a life-threatening or chronically debilitating disease and responds to an unmet need.

EMA said the program will be available for post-authorization data collection as well, although the agency does not specifically state whether such data collection efforts would be undertaken in pursuit of an expanded or additional indication for use.

EMA executive director Guido Rasi said, "Enabling patients' access to medicines is no longer a job for regulators alone. Today, we need to work with all decision-makers in health care to make sure that medicines that can make a real difference to people's lives can actually reach them." Rasi also said EMA's work with EUnetHTA "aims to align our respective requirements as much as possible so that developers can generate one set of data that allows the assessment of both the benefits and risks of a medicine and its added value."

EMA said the program will begin processing applications in September 2017. ♦

Product briefs

Brampton, Ontario-based **Medtronic Canada**, a subsidiary of Medtronic plc, received a Health Canada license and is launching its first and only magnetic resonance imaging (MRI) conditional cardiac resynchronization therapy defibrillators (CRT-Ds) for heart failure. The Medtronic Amplia MRI quad CRT-D Surescan and Compia MRI quad CRT-D Surescan systems are licensed for MRI scans on any part of the body without positioning restrictions. Now, patients in Canada with these devices have access to MRI scans if and when they need them. Both CRT-D systems are commercially available in Canada.

Osteoremedies LLC, of Germantown, Tenn., launched Floraseal microbial sealant through its U.S. distribution agreement with **Adhezion Biomedical LLC**, of Reading, Pa. Floraseal is a patented film-forming, cyanoacrylate-based microbial sealant to reduce the risk of skin flora contamination throughout surgery.

Roche Molecular Systems Inc., of Pleasanton, Calif., reported the commercial availability of the Avenio millisect system, a tissue dissection instrument that uses an automated digitally assisted process to reliably and efficiently isolate clinically relevant cells from formalin-fixed paraffin-embedded (FFPE) tissue slides. The Avenio millisect system is an IVD labeled medical device and is now available in the U.S. and countries accepting the CE mark.

Second Sight Medical Products Inc., Sylmar, Calif.-based developer of implantable visual prosthetics, reported market entry into Russia, implanting the first patient with the company's Argus II retinal prosthesis system in Moscow. The Argus II system provides electrical stimulation that bypasses the defunct retinal cells and stimulates remaining viable cells inducing visual perception in individuals with severe to profound retinitis pigmentosa. The implant was facilitated by the country's exclusive distribution partner, Medical Equipment Trading Co.

Seegene Inc., Seoul, South Korea-based developer of multiplex molecular diagnostics technologies and assays, said it will launch its Seegene random access system at the 69th AACC Annual Clinical Lab Expo in San Diego, July 30 to Aug. 3. The Seegene system can provide order-to-report on the same day by simultaneously performing high multiplex real-time PCR testing on a single platform, regardless of specimen type or assays.

Science

Continued from page 1

of drugs including hydroxyurea and 5-azacytosine increase levels of fetal Hb by turning on the Hb gene," noted lead researcher Merlin Crossley.

"The efficacy of these agents varies between patients and may decline over time in some individuals. Moreover, both are non-specific, also affecting other genes, so have side effects," said Crossley, professor of molecular biology in the School of Biotechnology and Biomolecular Sciences at UNSW in Sydney.

"Another treatment option involves bone marrow transplant from a healthy donor, but that donor must be well matched, which is a complicated procedure," he told *BioWorld MedTech*. Furthermore, "the lifelong cost of transfusion treatment is significant, as is pain, as SCA is a painful condition."

"Therefore there is a real need for new treatments," said Crossley, noting "at least one patient has been cured of thalassemia by gene therapy, involving gene replacement in stem cells in the blood," which offers a promising new therapeutic approach.

Genetic mutations affecting adult Hb production are among the most common of all variations, with approximately 5 percent of the world's population carrying a defective gene resulting in hemoglobinopathies, according to the WHO.

However, people with these diseases who also carry a beneficial natural mutation called British-198 have fewer symptoms of their disorder, because it turns on a fetal Hb gene normally turned off after birth.

The resulting extra fetal Hb, which has a particularly strong affinity for oxygen, then takes over the oxygen transportation function of the defective adult Hb.

"Fetal Hb has a very high affinity for oxygen to enable the fetus to extract oxygen from the mother's blood in utero," explained Crossley. "In adults, Hb with a lower oxygen affinity may be preferable, as this may be useful in delivering oxygen to other tissues.

"With CRISPR [clustered regularly interspersed short palindromic repeats] gene-editing, we can now precisely cut and alter single genes. We have shown that introducing the British-198 mutation into blood cells using CRISPR substantially boosts production of fetal Hb," he said. "Because this mutation is natural and benign, this organic gene therapy approach should be effective and safe to use to treat and possibly cure serious blood disorders."

However, more research is needed before it can be tested in people," he noted. Nevertheless, "I think we will see clinical trials beginning soon, as several groups are currently doing similar research with blood stem cells, although they tend to make gene deletions rather than substitution mutants, which can be done at a higher frequency."

Crossley's research team, which also comprised scientists from the Japanese Red Cross Society in Tokyo and the RIKEN BioResource Centre in Ibaraki, Japan, published their latest study's findings in the July 13, 2017, edition of *Blood*.

First identified in 1974, the beneficial British-198 mutation involves a change in just a single nucleotide in the genetic code. Carriers of this mutation have fetal Hb levels as high as 20 percent of total Hb, while fetal Hb levels usually fall to about 1 percent of total Hb after birth.

> *"Because this mutation is natural and benign, this organic gene therapy approach should be effective and safe to use to treat and possibly cure serious blood disorders.*
>
> Merlin Crossley
> Professor of molecular biology, School of Biotechnology and Biomolecular Sciences, University of New South Wales

The researchers used techniques including electrophoretic mobility shift assays to show that the British-198 mutation functions by creating a new binding site for the protein Krueppel-like factor 1 (KLF1), a transcription factor responsible for maturation of red blood cells, which turns blood genes on.

"This is the first time this has been demonstrated and is a key insight," said Crossley. "It shows how the gene sequence changes and how a new DNA-binding protein (KLF1) can bind, which is analogous to changing the lock on your front door and finding that a key meant for your neighbor's door now fits and lets you into your house."

This key discovery has significant implications for drug discovery and development, he noted. "If one could find a drug that encouraged KLF1 to bind to the unmutated site, or knocked off a repressor that binds nearby, that could be a useful new agent.

"KLF1 binds and turns on the fetal Hb gene, but there are also two repressors that turn it off. We are now studying those to see exactly what they do, with the hope of finding a way of inhibiting their activity at this gene locus," said Crossley.

In the future, "to turn the new gene editing approach into a therapy for blood disorders, the British-198 mutation would have to be introduced into blood-forming stem cells from the patient."

To achieve this "a large number of stem cells would have to be edited in order to repopulate the patients' blood with genetically enhanced cells," said Crossley.

"We did this gene editing in immortalized cell lines, by introducing CRISPR and a 'repair' DNA template. However, the same could also be done using purified stem cells, although these are rare and expensive." ♦

Owlstone

Continued from page 1

broadly aimed at every cancer known to scientists at England's prestigious Cambridge University.

The PAN Cancer Trial centers on Owlstone's unique, Reciva breath sampler that captures volatile organic compounds (VOCs) exhaled from the lungs, which can then be analyzed to identify biomarkers that signal disease.

The shared mission in the collaboration with leading cancer researchers at the Cancer Research UK (CRUK) Cambridge Center is to validate breath-borne biomarkers for the early detection of cancer.

With CRUK, the PAN Cancer Trial will sniff out the diagnostic potential of the Reciva device for bladder, breast, head and neck, kidney, esophageal, pancreatic, and prostate cancers and brain tumors.

Supporting this breath-taking sweep of research are the University of Cambridge and Cambridge University Hospitals NHS Foundation Trust.

Owlstone already has two trials underway to validate biomarkers it has identified for lung and colorectal cancer. (See *BioWorld MedTech*, Oct. 5, 2016.)

Patients with a suspected cancer referred to Addenbrooke's Hospital on the standard NHS cancer care pathway will be asked to give a breath sample in addition to routine tests.

These samples will be carted across campus to Owlstone's Cambridge facility for analysis of the captured VOCs using its breath biopsy platform, which has demonstrated a high sensitivity and selectivity across a range of diseases.

The breath samples of patients with, and without, cancer will be assessed to determine whether reliable biomarkers for early diagnosis of cancer can be identified.

"No one has undertaken a study of this scale, to understand potential biomarkers across as many cancer types," Owlstone Medical CEO Billy Boyle told *BioWorld MedTech*.

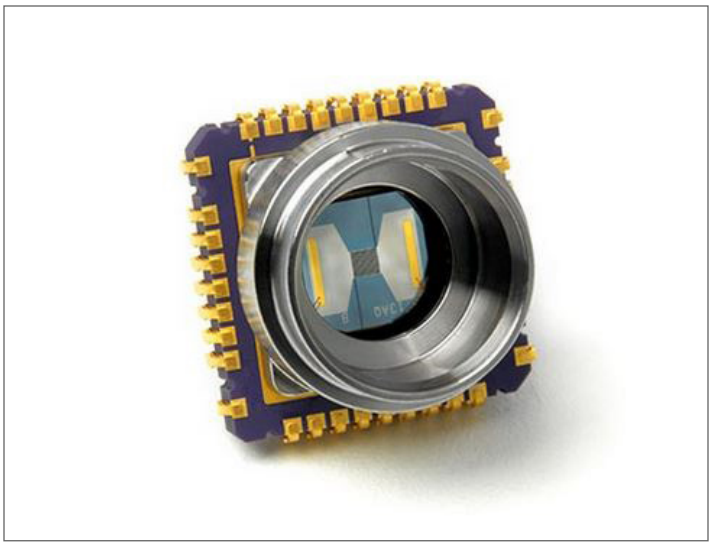
"There have been a lot of smaller, piecemeal studies. We are the ones bringing it all together, to get the best understanding of how breath biopsy and VOCs can be used in the detection of multiple tumor types," he said.

The chief investigator for the PAN Cancer Trial, Professor Rebecca Fitzgerald, called the program "a flagship initiative of the CRUK Cambridge Center that aims to devise better means of detecting cancer and diagnosing it in the early stages, which can lead to improved outcomes for cancer patients."

The trial will begin with a pilot phase.

"We are still designing clinical protocols as there are different tumor types, and different patient populations. Once this first step is completed it will inform planning for a larger study. What will determine how fast a given study can go will be how many patients come through the doors at the clinic," said Boyle.

Created as a spinout from Owlstone Inc. in 2016 to focus on medical applications for a novel chemical detector developed at Cambridge, Owlstone Medical holds several advantages in tackling the ambitious PAN Cancer Trial.



FAIMS microchip; Owlstone Medical Ltd.

> *"Blood is the key in all of this. Cancer has a metabolism even at early stages, there are metabolites being produced and passed into the blood. The smallest components can pass from the blood to the airways.*
>
> Billy Boyle
> CEO, Owlstone Medical

"The company was commercial from day one," said Boyle, generating a revenue stream from the CE marked Reciva device for capturing VOCs, as well as sales of the instrument and consumables for analysis.

Owlstone also generates revenue from collaborative partnerships with pharmaceutical companies utilizing its technology to monitor patients in drug trials for asthma and chronic obstructive pulmonary disease (COPD).

And six months after its start up, Owlstone Medical had raised £19.3 million (US$23.5 million) through private placements.

Meanwhile the parent company has a thriving business for chemical detection with governments, academic centers, major companies in pharmaceutics, oil, food and beverage, or security, such as the United States Department of Defense and the U.S. Army.

According to Boyle, "Breath biopsy is a new modality, so the logic of what we are trying to do here is to get as much of a detailed understanding of the biomarkers for multiple cancers, disentangling which biomarkers relate to cancer more generally versus those which have some specificity to identify the cancer site."

"When you look at breath, you see thousands of chemicals, and you wonder where all this is coming from. Some come from

See Owlstone, page 9

Owlstone

Continued from page 8

the airways, but 80 percent of them come from the blood. Our lungs are very good for exchanging oxygen and carbon dioxide, but also for expressing volatile organic compounds," he said.

"Blood is the key in all of this. Cancer has a metabolism even at early stages, there are metabolites being produced and passed into the blood. The smallest components can pass from the blood to the airways," he said.

The VOCs in the breath sample are captured by an absorbent material packed in metal tubes for handling. Once loaded in the analyzer instrument, the material is heated to free the VOCs, which are studied using the company's proprietary Field Asymmetric Ion Mobility Spectrometry (FAIMS) technology, a method of distinguishing charged gaseous molecules under the influence of an oscillating electric field.

He said the company's heritage working with leading global organizations means it has the knowledge and experience with the technology to maintain good stability and repeatability over time.

Breath biopsy belongs to the next generation of metabolomic lab diagnostics where no sample preparation is required, no clinical chemistry needed to precipitate a reaction with reagents, and the process boils down to pure data.

"The real discovery work is happening at the software level. The team of data scientists we have is our fastest-growing group, the ones who are able to turn raw data sets into meaningful information about what markers or set of markers may be related to a specific disease," said Boyle.

He acknowledged that, "The limitation is the compounds need to be volatile, they need to be expressed on the breath. There are some areas where breath sampling will not work, those elements of the blood that will not be volatile."

Here there is a need for a blood-specific analysis, he said.

"We don't believe there is one magical technology that is going to solve all the problems. Breath biopsy is one approach. Liquid biopsy markers have a role to play, NMR (nuclear magnetic resonance) with urine samples has a role to play as well," he said. (See *BioWorld MedTech*, July 25, 2017.)

"We all know the destination we are trying to get to, which is the early detection of cancer, and taking different approaches creates a higher probability that we will get there," he said. ♦

Product briefs

Sensus Healthcare Inc., of Boca Raton, Fla., reported its SRT-100 has been cleared by the China Food and Drug Administration to treat and prevent keloids. The company's partner in China is Chindex Medical Ltd., a wholly owned subsidiary of Fosun Pharma International. Chindex Medical plans to launch the SRT-100 for the treatment of keloids into the market during the fourth quarter of 2017, with a focus on preventing and treating keloids associated with Cesarean sections. Chindex Medical has been selling the SRT-100 in China for the treatment of nonmelanoma skin cancer since 2014.

Sequoia Sciences Inc., of St. Louis, received fast track designation from the U.S. FDA for its investigational vaccine designed to treat recurrent urinary tract infections (UTI) caused by multidrug-resistant bacteria. Sequoia's vaccine is designed to create an immune response preventing bacteria from colonizing the urinary tract, and it recently completed its first clinical trial in women.

The Spectranetics Corp., of Colorado Springs, Colo., won a PMA for its Stellarex drug-coated balloon. The ballon is intended to for patients with peripheral artery disease to restore and maintain blood flow to the superficial femoral and popliteal arteries.

Surmodics Inc., of Eden Prairie, Minn., said it received an investigational device exemption from the U.S. FDA to initiate a pivotal clinical trial of the Surveil drug-coated balloon (DCB). The randomized trial will evaluate the safety and effectiveness of the Surveil DCB for treatment for peripheral artery disease in the upper leg compared to the Medtronic In.Pact admiral DCB. The clinical study will be used to support regulatory approvals and reimbursement.

Tongue Lab Europe Ltd., Paris-based maker of the TRP (Tongue right positioner), launched its first clinical trial to evaluate the benefits of the TRP on snoring. The TRP is a custom-fitted oral device that enables the tongue to return to its physiological functions and positions, thus increasing muscle tone. Thirty-five men and women who have been diagnosed as chronic snorers will be enrolled in the study, which will be conducted over nine months in Prague. Every three months, their snoring levels will be measured to evaluate the consequences of wearing the TRP while sleeping.

Regulatory front

The **Centers for Medicare & Medicaid Services** proposed to cut payments to home health agencies by roughly $80 million in 2018, a reduction of 0.4 percent over the current calendar year. The agency's draft prospective payment proposal for home health would boost payment by one percent to home health agencies that report quality data, but would offset that with a 2 percent reduction to HHAs that do not report quality data and with a 0.97 percent reduction to the standardized 60-day episode rate to account for changes in case mix seen in data from 2012-2014. The 60-day episode method would be switched to a 30-day episode in 2019, although this will not be accompanied by any change to the split-percentage payment approach until after the agency has obtained feedback on any such changes. CMS said it will revisit the data elements used to measure treatments for pressure ulcers, and that it wants to "start a national conversation" about how the agency can make health care "less bureaucratic and complex." To that end, CMS will solicit opinion aimed at payment system redesign and elimination or reduction of reporting burdens, among other possible changes. The agency is taking comment through Sept. 25.

Regulatory front

Fujifilm Medical Systems USA of Stamford, Conn., issued a notice of urgent device correction/removal for the company's ED-530XT duodenoscope to allow the company to replace several device components, including the device elevator and O-ring. The FDA had previously advised companies making duodenoscopes that some system components were designed such that these devices were difficult to adequately sterilize between uses, which was blamed on a number of infections. Fuji said the FDA approved the new design July 21, and that all customers will have completely updated devices by October.

The **European Medicines Agency** said it will partly or fully suspend the marketing authorization for three gadolinium-based MRI imaging agents based on the recommendations of the agency's Pharmacovigilance Risk Assessment Committee. The committee had determined that there is evidence that some gadolinium-based contrast agents leave deposits in the brain, but did not identify any pathologies associated with those deposits. EMA completely suspended the marketing authorizations for two linear gadoliniums, while restricting the routes administration or indications for use for two others, including Magnevist (gadopentetate), which will henceforth be authorized only for intra-articular administration. The **FDA** had concluded in May that while there was evidence of some accumulation of deposits in various tissues, the only condition attributed to such deposits was nephrogenic systemic fibrosis, which the agency said was seen in only a small group of kidney failure patients. Despite the bad news for linear gadolinium agents, the macrocyclic variants were untouched by the EMA action.

The **FDA** said it has scheduled the first-ever meeting of the agency's patient engagement advisory committee for medical devices, set for Oct. 11-12, 2017, when the committee will be queried on patient input in device clinical trials. The meeting will run a full day on Oct. 12, but only in the afternoon of the 11th, and will be held at the Hilton Washington DC North in Gaithersburg, Md. The hearing will take comment on challenges facing patients involved in device trials and how sponsors and the agency can address those challenges. The advisory committee will consist in part of Paul Conway, president of the American Association of Kidney Patients, and Deborah Cornwall, who has served on a volunteer basis for the American Cancer Society.

The FDA's **Center for Devices and Radiological Health** will host an Oct. 10, meeting at the agency's campus in Silver Spring, Md., to review a voluntary pilot program for independent assessments of device manufacturing and product quality. The agency said its collaboration with the Medical Device Innovation Consortium has yielded a maturity model and appraisal system devised by the CMMI Institute of Pittsburgh, which will be used in the pilot program. The agency said this process is not intended as a substitute for a quality systems inspection, but instead is intended to be a "driver of continuous process and product improvement."

The **Medicare Payment Advisory Commission** said in its most recent data book for health care spending that Medicare was the largest single purchaser of health care services in 2015 at 22 percent, although private payers in the aggregate counted for 35 percent of spending. In 2006, inpatient hospital spending accounted for 31 percent of the $402 billion in Medicare spending ($124 billion), but only 22 percent of the $638 billion in 2015 ($140 billion). Medicare spending on clinical lab services reached $9.2 billion in both 2012 and 2013, but fell to $8.8 billion in 2015. As previous reports suggest, small percentages of enrollees account for disproportionate shares of Medicare spending, with the top one percent consuming 17 percent of Medicare expenditures, and the top 5 percent accounting for 42 percent of spending. The report projects that Medicare enrollment will reach 80 million by 2032, and that there will be only 2.4 workers per beneficiary by 2029. Medicare spending is predicted to reach $1 trillion by 2021 or 2022.

Orthopedics Extra

Keeping you up to date on recent developments in orthopedics

By Holland Johnson, Executive Editor

Study finds obese patients don't need to lose weight before total joint replacement

A new study from the University of Massachusetts Medical School found that obese patients who underwent knee or hip replacement surgery reported virtually the same pain relief and improved function as normal-weight joint replacement patients six months after surgery. "Our data shows it's not necessary to ask patients to lose weight prior to surgery," said Wenjun Li, associate professor of medicine and lead author on the study. "It's challenging for a patient who is severely overweight and suffering in pain to exercise – often they just can't do it. Our evidence showed that severe morbidly obese patients can benefit almost equally as normal weight patients in pain relief and gains in physical function." The aim of the study, published July 19 in the *Journal of Bone and Joint Surgery*, was to evaluate the extent of pain relief and functional improvement in total joint replacement patients with various levels of obesity. The researchers concluded that while obesity is associated with a greater risk of early complications, obesity in itself should not be a deterrent to undergoing total joint replacement to relieve symptoms. Preoperative and six-month postoperative data on function, joint pain and body mass index (BMI) from a national sample of 2,040 patients who had undergone total hip replacement and 2,964 who had undergone total knee replacement from May 2011 to March 2013 was collected. Preoperative and postoperative function and pain were evaluated according to BMI status, defined as under or of normal weight, overweight, obese, severely obese, or morbidly obese. A greater obesity level was associated with worse pain at baseline but greater postoperative pain relief, with average postoperative pain scores at six months similar across the BMI levels. "This surprised us a little bit. Past analysis showed that obesity is associated with outcomes to some degree, but here we see the magnitude is so small it won't make much difference, and severely obese patients can benefit a lot from the surgery," said Li. "Patients who can lose weight should, but we acknowledge many people can't, or it will take a long time during which their joints will worsen. If they can get the surgery earlier, once function is restored they can better address obesity." The article is titled "Functional gain and pain relief after total joint replacement according to obesity status."

Opioid prescription rates for OA remained stable despite increased awareness of risks

Recently published results showed the rates of prescribing opioids for osteoarthritis remained stable between 2007 and 2014, despite the increased awareness of opioid risks. Researchers queried the Humana Inc. administrative claims database from 2007 to 2014 and identified all patients with either hip, knee or any joint osteoarthritis (OA). Researchers reviewed claims data to identify opioid prescriptions associated with a diagnosis of OA, trending the rates of prescribing with time and stratifying results by sex, age and geographic region in the U.S. Results showed 11.5 percent of patients with OA will receive an opioid prescription per year. Researchers noted opioids were more likely prescribed to patients with OA of any joint versus patients with knee or hip OA, and among patients with knee OA vs. patients with hip OA. For all OA groups, men and patients who were 49 years or younger were more likely to receive an opioid prescription. However, researchers found no differences based on sex in the OA in any joint group. The lowest odds of receiving an opioid prescription for hip OA, knee OA and OA of any joint was found among patients in the Northeast, while the highest odds were found among patients in the South. Researchers noted the South and West had no significant differences in the odds of receiving an opioid prescription for hip and knee OA. The article, titled "Are we still prescribing opioids for osteoarthritis?" was published in the July issue of the *Journal of Arthroplasty.*

AJRR releases annual report for patients about hip, knee replacement surgery

The American Joint Replacement Registry recently published the 2016 Report to the Public About Hip and Knee Replacements, which is a patient summary of clinical data found in its annual report. According to the report, the AJRR found a significant increase in the use of ceramic femoral heads, with a higher percentage of ceramic heads being used for younger patients compared with older patients. The report also noted a "marginally significant increase" in the percentage of total hip arthroplasties performed for femoral neck fractures vs. hemiarthroplasty from 2012 to 2015. During the same period, the use of modular neck stems decreased while the use of dual mobility liners increased, according to the report. In addition, the report showed a slight downward trend in the use of unicompartmental knee implants. Approximately 30 percent of surgeons reported performing unicompartmental arthroplasty in 2015, while patellofemoral arthroplasty represented less than 1 percent of knee arthroplasties. The report noted a significant increase in the use of antioxidant polyethylene acetabular liners from 2012 to 2015 for both the hip and knee data. The AJRR also noted a revision burden of 10.2 percent among hips and of 8.7 percent among knees, which was consistent with the values reported for other large national registries.