MEDICAL DEVICE DAILY™

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COIN-SIZED, LEADLESS IMPLANT

Valencia Technologies to launch IDE study for drug-resistant hypertension device

By Amanda Pedersen, Senior Staff Writer

As interest in device-based hypertension therapies continues to grow, the U.S. FDA has given Valencia Technologies Corp. the go-ahead, as soon as certain conditions are met, to start an investigational device exemption (IDE) pivotal study of its nickel-sized neurostimulator for drug-resistant hypertension. The device is designed to use low-duty cycle current to stimulate the median nerve once a week for 30 minutes – without any leads.

The Valencia, Calif.-based company has designed the study to enroll 306 patients who are on at least three anti-hypertensive drugs. The leadless neurostimulator is implanted in each forearm during a 20-minute office procedure (10 minutes per arm)

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SHINING A LIGHT ON CANCER

Clearlight Diagnostics partners with OCSSB for a closer look at pancreatic cancer

By Omar Ford, Staff Writer

There is a dire need for more effective tools to diagnose pancreatic cancer. The disease is often discovered in its later stages, which significantly impacts therapy effectiveness. A collaboration between Sunnyvale, Calif.-based, Clearlight Diagnostics

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REGULATORY

Test maker blasts rate cut proposed for heart transplant rejection test

By Mark McCarty, Regulatory Editor

Medicare administrative contractors (MACs) can exercise a fair amount of discretion in terms of coverage, but reimbursement discretion has rarely shown up in the area of tests for rejection of heart transplants. Peter Maag, president and CEO of Caredx, told *Medical Device Daily* that at least four

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BACKWATER TO BEACHFRONT

Nobel Prize goes for autophagy research

By Anette Breindl, Senior Science Editor

"Basically, it's not easy to define what will serve humanity."

So said Yoshinori Ohsumi, honorary professor at the Tokyo Institute of Technology, after winning the 2012 Kyoto Prize in Life Sciences for his research.

The Nobel Assembly followed suit in recognizing the importance of Ohsumi's work, awarding him the 2016 Nobel Prize in Physiology or Medicine to "for his

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EARLY-STAGE CANCER TOOL

A new generation of intraoperative probes emerge for radio-guided surgery market

By Bernard Banga, Contributing Writer

Forimtech SA, of Geneva, Switzerland, has developed a new generation of lightweight, compact, wireless probes that can track down cancer cells and suspicious-looking lymph nodes during operations. This technology has been CE marked since last year and is currently

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CARDIOLOGY EXTRA

Senior Staff Writer Amanda Pedersen on one of med-tech's key sectors

Read this week's Tuesday Special

OTHER NEWS TO NOTE

Exosome Diagnostics Inc., of Cambridge, Mass., has entered into an agreement with **Amgen Manufacturing Ltd**., of Thousand Oaks, Calif., to evaluate the potential to advance drug development with Exosome's liquid biopsy diagnostics technology and platform. The companies will collaborate to identify a potential liquid biopsy diagnostic. Financial terms of the agreement were not disclosed.

Invitae Corp., of San Francisco, a genetic information company, said the U.S. **Centers for Medicare and Medicaid Services** (CMS) announced final pricing for genetic testing for hereditary breast cancer-related disorders. The tests are billed under the new current procedure terminology (CPT) code 81432, which became effective on Jan. 1. CMS had previously reported a temporary payment per test of $622.53, and – after a public comment period – the final payment per test is now set at $925. Payments are made by Noridian, CMS's administrative contractor for California.

Medfusion Inc., of Cary, N.C., a provider of patient experience solutions, said Chicago-based, **GE Healthcare Inc.**, has named the company as the inaugural member of its Centricity Partner Program. GE Healthcare's Centricity Partner Program recognizes Centricity software and services partners and enables them to collaboratively test software and services with GE Healthcare solutions.

Neotract Inc., of Pleasanton, Calif., reported new positive coverage decisions from Geisinger Health Plan and Emblemhealth, expanding access to the Urolift System for the treatment of their members with benign prostatic hyperplasia.

SBRI Healthcare,of Cambridge, U.K., an NHS England-funded initiative to develop innovative products that address unmet health needs, said five companies that have successfully reached the next phase (phase 2) of the clinically-led competition. Improved management of continence, monitoring and support in the home, and a dynamic new powered wheel chair have been selected with each successful company receiving financial backing of up to £1 million to develop products that focus on addressing the challenges faced by older people suffering with complex health conditions.

PRODUCT BRIEFS

Edwards Lifesciences Corp., of Irvine, Calif., received CE marking for its Acumen Hypotension Probability Indicator (HPI), a technology designed to alert clinicians to potential hypotension, or abnormally low blood pressure, in surgical and critical care patients before it occurs. The HPI is part of the company's Acumen decision-support software suite and is only compatible with Edwards' hemodynamic monitoring technology.

Fortimedix Surgical BV, of Nuth, the Netherlands, received CE marking for Fmx314, the company's single-port surgery solution that is compatible with a standard 15 mm trocar for use in minimally invasive abdominal laparoscopic surgery. According to the company, the device is designed to provide a platform solution that is small, simple, and secure for laparoscopic surgery. The company expects to launch the device in the U.S. later this month and in Europe next year.

South San Francisco-based **Profusa Inc.** received CE marking for its Lumee Oxygen Platform for continuous, real-time monitoring of tissue oxygen. The company said it will initially sell the system for monitoring tissue oxygen in the treatment of peripheral artery disease.

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Valencia

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under local anesthesia, where it sits over the tendons and is able to access the median nerve. The patient is sent home with the arm wrapped and prescribed topical creams to prevent infection while the scar heals.

The goal of the study is to examine the treatment effect after six months of therapy. The treatment group will be compared against a sham-control group. The study will allow all enrolled patients to receive the potential benefits of the therapy, as the control group members will have their devices activated at the six-month point. All study patients will be monitored for an additional 18 months.

Reid Gormly, manager of investor relations and the OUS clinical trials associate at Valencia, told *Medical Device Daily* the company was founded in 2011, right as interest in device-based therapies for hypertension – namely, renal denervation – was really heating up.

Taking note of what other companies were doing to address drug-resistant hypertension, Valencia's founders saw an opportunity to be competitive in that market by developing a potentially smaller, safer and cheaper device that would avoid all of the major arteries, Gormly said. The company recently completed a study overseas that met all of its endpoints, he said, and the results of that 48-patient trial will be reported during the upcoming Transcatheter Cardiovascular Therapeutics meeting at the end of the month in Washington.

By placing the device just underneath the skin to activate the median nerve, the company said the Ecoin is designed to send out electrical stimulus that communicates with the brain. The signal has multiple pathways to the brain's blood pressure control center, the company said, with the goal of creating a normalizing effect on blood pressure.

Gormly said Valencia has been working with the FDA for a little over a year to determine the Ecoin's U.S. pathway, and the U.S. study will mimic the design of the company's overseas study very closely.

A BLINDING CHALLENGE

Designing a double-blinded study to evaluate a device that is designed to stimulate a patients' nerves presents somewhat of a unique challenge, but Gormly said the company's previous study proved that the challenge was easy to overcome.

First, he said, all patients in the trial are required to go through a fitting session during which an engineer turns the device on to determine the ideal setting parameters for that individual, and then turns the device off if the patient is randomized to the sham arm.

Also, not all patients are expected to feel the once-a-week stimulation – even if they are randomized to the active study arm – so a patient who doesn't feel the stimulation would not necessarily know which group they were assigned to. Naturally, patients will try to guess which arm of the study they are in, but their predictions have proven to be a bit off the mark.

"We have patients on video who thought they were getting the therapy and they actually weren't, or vice versa," Gormly said, referring to patients who participated in the company's overseas study.

THE TROUBLE WITH DRUGS

While there seems to be a wide variety of approaches under development for hypertension – particularly for patients who do not seem to tolerate, respond well, or comply with prescribed medication – it is not hard to understand the growing interest in finding a device-based solution to this problem.

Atul Chugh, an attending cardiologist at St. Francis Hospital in Indianapolis, said most of his patients understand the ill effects of hypertension but many of them find it difficult to take their prescribed anti-hypertensive drugs either due to financial restraints or intolerable side effects. Chugh said the "holy grail" of hypertension management therefore lies in a therapy that is both cost-effective and easily tolerated.

Valencia's device may prove to be both.

Gormly said the company's overseas study resulted in only two device-related adverse safety events and that both of those cases were due to infections acquired at the trial site that resulted in the device being removed. There were also 13 minor safety events documented, he said, but those were primarily numbness, swelling, and redness at the implantation site that cleared up and did not require the device to be explanted.

He also noted that the device itself is designed to be produced at a low cost and ultimately may end up being cheaper than current anti-hypertensive drugs on the market. The device can be produced for hundreds of dollars versus thousands, Gormly said, however the company has not yet set a price point for the product.

The battery life of the device is roughly three to five years, depending on the stimulation setting, he said.

The company noted that the device can be implanted near various target nerves, making it a potential treatment option for a number of other chronic conditions in the future, including heart failure, overactive bladder, and osteoarthritis of the knee. //

DAILY M&A

Bowie, Md.-based **Inovalon Holdings Inc.**, a company providing cloud-based analytics and data-driven intervention platforms to the health care industry, has completed its previously reported acquisition of Canonsburg, Pa.-based Creehan Holding Co. Inc., the parent company of Creehan & Company, an independent provider of specialty pharmacy and specialty medications management software-as-a-service (SaaS) platforms. All customary closing conditions have been satisfied and antitrust clearance has been received.

Clearlight

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LLC and Oregon Health & Science University Center for Spatial Systems Biomedicine (OCSSB) could ultimately result in the development of a diagnostic product that could give oncologists a stronger understanding of the disease.

Clearlight Diagnostics, a private company, said its goal is to use methods for tissue processing and 3-D light-sheet microscopy, to develop biomarkers to map key aspects of pancreatic cancer. The company called the partnership with OCSSB, a "milestone" and said this was the very first research collaboration it has had since it formed a little more than a year ago.

"I think coming out of [the collaboration with OCSSB), we would like to have identified a panel of biomarkers within the pancreatic cancer microenvironment," Laurie Goodman, chief scientific officer of Clearlight Diagnostics, told *Medical Device Daily*.

To do this, the company will use OCSSB's knowledge in the area of pancreatic research to lead to the development of these key pancreatic cancer biomarkers. In addition the company will use its core technologies, Clarity and Colm, which were developed by its founder, Karl Deisseroth and colleagues at Stanford-Calif.-based Stanford University.

Clarity is a tissue clarification method that uses chemical treatments to render tissue optically transparent for microscopy and sample analysis. Clarity enables the transformation of tissue into a nanoporous, hydrogel-hybridized form that is cross-linked to a three-dimensional network of hydrophilic polymers. The process produces a fully assembled, intact tissue, which is permeable to macromolecules and optically transparent, thus allowing for three-dimensional imaging of subcellular components (DNA, RNA and protein) and heterogeneous cellular interactions within the tumor microenvironment.

Clear Diagnostic's Colm is an optics system for accelerating image collection from clarified samples. It visualizes labeled tissue elements, cells and connections within tissue blocks.

OCSSB said Clearlight Diagnostic's technology could give insight on tumor-microenvironment interactions, which could in turn, strongly influence therapeutic response. The organization said through its collaboration with Clearlight Diagnostics it could use information derived from the research to devise therapeutic approaches that counter microenvironmental mediated resistance.

Already companies are scrambling to develop a more effective means of treating pancreatic cancer. While pharmaceutical solutions are traditionally the standard route in treating pancreatic cancer, Novocure ltd, is going a slightly different route by incorporating a device into the treatment of patients. The St. Helier, Jersey Isle-based company is developing the Novottf-100L(P) system and will release results from the 40-patient PANOVA, pilot trial in December. In the study, the Novottf-100L(P) system will be used in patients with pancreatic cancer which is not amenable to surgical resection, when the device is combined with standard chemotherapy for pancreatic cancer. The device administers Ttfields to patients concomitantly to the best standard of care treatments which would normally be used to treat their pancreatic cancer – gemcitabine or nab-paclitaxel (brand name: abraxane).

"We expect that the PANOVA data will be watched closely," said Larry Biegelsen, an analyst with Wells Fargo.

But while data from PANOVA is only a few months away, the time line for research derived from Clearlight and OCSSB will be a lot longer Goodman said.

"We're in the research and develop phase of the company," Goodman said. "We want to develop a platform that can be used by academics in conjunction with pharma to help support drug development and cancer research."

The company said that even though it might take a few years to get a product to the FDA to review, it still had strong support from investors. Just last year, the company raised $2.58 million in equity financing.

"We've been helping our investors understand the value of what we're bringing in cancer research," Goodman said. **//**

APPOINTMENTS AND ADVANCEMENTS

New York-based **Acuamark Diagnostics Inc.**, a company developing blood-based screening tests for the early detection of cancer, reported that Brian Carr has been appointed to its board. Carr started his laboratory career with Allied Clinical Laboratories before forming Informdx, which later merged with Ameripath. Carr subsequently served as president and board director of Ameripath before co-founding and becoming chairman and CEO of American Esoteric Laboratories, later acquired by Sonic Healthcare Limited, a publicly held Australian diagnostics company. Carr then served as a co-founder and CEO of OralDNA Labs, a privately held salivary diagnostic company which was acquired by Quest Diagnostics in May 2009.

Nuvasive Inc., of San Diego, Calif. reported that Joan Stafslien is joining the company as executive vice president, general counsel and corporate secretary. Stafslien joins Nuvasive from Carefusion, where she served as general counsel and corporate secretary from 2009 until its acquisition by Becton Dickinson in 2015. Nuvasive is a developer of minimally invasive, procedurally-integrated spine solutions.

Regulatory

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MACs have proposed reductions to rates paid the CPT code for the company's Allomap test for heart transplant failure, one of which would reduce the previous payment level of roughly $2,800 by about one third.

Caredx of Brisbane, Calif., announced in July that Novitas Solutions of Mechanicsburg, Pa., had proposed to "drastically cut" rates for the Allomap test, but the U.S. Centers for Medicare & Medicaid Services announced in 2015 it would subject CPT code 81595 to gapfilling for the purposes of the calendar year 2016 clinical lab fee schedule. The rates proposed by the MACs are often averaged by CMS to arrive at a reimbursement level across the nation for a given test.

Maag said each of the eight MACs charged with Part B billings had submitted their prices, adding that Novitas had initially filed the lowest price among the four MACs that had proposed a lower reimbursement rate. The list includes First Coast Service Options, the Jacksonville, Fla.-based MAC charged with the state of Florida, but Novitas has proposed a reduction in reimbursement from the previous set point of roughly $2,820 to $1,920, which comes to a cut of about 32 percent.

The company won a 510(k) clearance for the test in 2008, and Caredx said it has continued to invest in the test, and that it has yet to fully amortize the associated research and development.

Maag said the four MACs that had proposed lower rates "have no experience with Allomap," while the four MACs he said have had experience with the test have submitted reimbursement rate proposals to CMS that reflect the established pricing benchmark. He said none of the MACs that had proposed lower rates had attempted to explain how they arrived at those metrics. Maag said Novitas had previously floated a reimbursement amount of $730, but stated, "there is no private payer contract that's below the $2,821 figure."

The predicament is not entirely novel, as Maag said the MACs had proposed lower payment levels last year as well, although the company managed to fend off the proposed rate changes. However, he suggested that the MACs that are proposing significantly lower rates are stepping outside their areas of expertise. "The one MAC that has the mandate to price these tests ... is Palmetto [GBA], and Palmetto has priced these tests adequately," Maag said, adding, "you might find that there is a battle between Novitas and Palmetto as to who has the authority to price these tests."

Maag said the company is covering its operating costs, but has yet to fully recoup the research and development costs associated with the test. "We now have 30 days to overturn this. We will move heaven and earth to make that happen," he said, adding, "for us, it's a matter of survival."

Jon Kobashigawa, associate director of the Cedars-Sinai Heart Institute in Los Angeles, told *Medical Device Daily*, "we're very concerned about access," to the Allomap test. He said the alternative to the test, which is heart biopsy, is conducted via the internal jugular vein, adding that a patient might have to undergo between 15 and 20 such procedures in the first year post-transplant.

Kobashigawa said the biopsy is very uncomfortable and can cost three to five times more than the rates currently paid for the Allomap. Given a choice, he said, "100 percent of patients would want that blood test," Kobashigawa said, noting that he was the principal investigator of a study of the test.

Assuming the proposed pricing cuts go through, "the patients will have to go back to biopsy, which is crazy," Kobashigawa said, adding that most heart transplant programs are using the Allomap in lieu of biopsy. He remarked that biopsy requires the use of a chest X-ray post-procedurally to ensure nothing went awry during the course of the biopsy, another hazard for a sick patient population to endure. "The company cannot exist with such a low reimbursement rate," he added, arguing that it should not be on the hospital to cover the difference between Medicare rates and what the company needs to continue operations.

Kobashigawa said he was aware of this same issue as it arose last year and that several medical societies in the U.S. and in other nations had voiced their support of the then-standing reimbursement rate. //

Nobel

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discoveries of mechanisms for autophagy."

Autophagy, or the process of self-eating, is an excellent example of a process whose understanding may end up serving humanity in multiple ways. It is now being recognized as a basic cellular process that plays a role in many different diseases.

But when Ohsumi began his research, nearly 30 years ago, autophagy was more or less a research backwater.

The freshly minted Nobelist said that "When I started my work, probably every year 20 or [fewer] papers appeared on autophagy." But "as research into autophagy has expanded, it has become clear that it is not simply a response to starvation. It also contributes to a range of physiological functions, such as inhibiting cancer cells and aging, eliminating pathogens and cleaning the insides of cells."

As a result, there are now several thousand papers a year published on autophagy, and researchers are trying to target the process in disease states including cancer, infectious diseases and neurodegeneration.

Autophagy is a cellular response that attempts to deal with stress, often induced by starvation. When nutrients are scarce, cells will recycle large cytoplasmic proteins and organelles to survive until the situation improves.

INFECTIOUS DISEASE

The process plays a role in infectious diseases, where either blocking or encouraging it can be useful, depending on the exact situation. Some infectious agents, such as *Mycobacterium tuberculosis*, block autophagy in macrophages to protect themselves from being digested. This ultimately prevents antigen-presenting cells from having anything to present and allows *M. tuberculosis* to hide itself from the immune system.

The malaria parasite, on the other hand, uses autophagy to remodel itself during the transition from liver to blood stage of infection and the malaria hydroxychloroquine blocks autophagy.

Cancer researchers have become interested in blocking autophagy because it is one way in which cancer cells can find material to fuel their growth. Autophagy is one of the processes that are linked to the activity of mTOR, a major sensing complex that directs growth decisions according to nutrient availability. When nutrients are plenty, mTOR will inhibit autophagy. Conversely, when mTOR is inhibited, cells can use autophagy as an alternate path to fuel.

As a result, hydroxychloroquine is currently enjoying something of a second career in oncology.

Everolimus (RAD001, Novartis AG) and Torisel (temsirolimus, Pfizer Inc.), both mTOR inhibitors, are being tested in separate phase I trials in combination with hydroxychloroquine. Other phase I trials are looking at the effects of adding hydroxychloroquine to HDAC inhibitor Zolinza (vorinostat, Merck and Co. Inc.), proteasome inhibitor Velcade (bortezomib, Takeda Oncology Co.), and radiation. And furthest along is a phase II trial comparing Tarceva (erlotinib, Roche Holding AG) with and without hydroxychloroquine in EGFR-mutated non-small cell lung cancer.

However, just as either blocking or upping autophagy can be useful in infectious diseases, the role of autophagy in cancer is complex.

While established tumors use autophagy to feed themselves, autophagy appears to be a tumor suppressor mechanism earlier in the game.

In a 2015 review article published in *Leukemia*, researchers from the University of Pittsburgh Medical Center summarized the situation by saying that "during the early phase of tumor initiation, autophagy appears to be suppressed, allowing the emergence of genomic instability. Later in tumor development, autophagy is more active, leading to enhanced cancer cell survival, as described in this review. Therefore, efforts to inhibit autophagy are particularly warranted in established tumors."

NEURODEGENERATION

While autophagy inhibitors are being tested in cancer, at least one cancer drug – Tasigna (nilotinib, Novartis AG) increases autophagy. Tasigna also crosses the blood-brain barrier, and so it is being tested in neurodegeneration, where increasing autophagy may be a promising strategy.

Many neurodegenerative diseases result from the accumulation of misfolded proteins, such as amyloid plaques in Alzheimer's disease, alpha-synuclein clumps in Parkinson's, and misfolded prion proteins. Rare diseases, such as lysosomal storage disorders, also result in part from mutations that lead to the production of proteins that first misfold, and then aggregate.

One of the problems with such aggregations is that they become too big to enter the cellular trash disposal system that would normally break them down, the ubiquitin-proteasome system.

They can still, however, be dealt with via autophagy, which is specialized on larger molecules.

A phase I trial by researchers from Georgetown University showed that in a phase I trial, treatment with Tasigna "increased brain dopamine and reduced toxic proteins linked to disease progression in patients with Parkinson's disease or dementia with Lewy bodies," according to a statement by the university's press office.

The trial also made enough of a splash that the National Parkinson's Foundation weighed in, releasing a statement that Tasigna "had positive results that certainly warrant the

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Forimtech

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being tested by surgeons at Lausanne University Hospital (CHUV) and throughout Europe.

Surgical radio-guided procedures have been used for many years and involve injecting patients with radioactive isotopes, which emit beta- (positrons or electrons) or gamma-particles. These isotopes preferentially bind to diseased tissues (e.g. tumors) via their carrier molecules. This type of radio-guided surgery is widely recognized for treating breast cancer, melanoma, thyroid, neuroendocrine and several other types of cancer. Intra-operative probes for oncological radio-guided surgery are widely recognized, very helpful tools that complement diagnostic equipment such as PET/CT and SPECT/CT scanners. The probes make further use of radiopharmaceuticals already administered to patients for pre-operative scans, guiding surgeons to 'hot spots' during open surgery.

"Nevertheless, the International Atomic Energy Agency (IAEA) acknowledged in its latest publication on guided intra-operative scintigraphic tumor targeting that there is a lack of adequate devices on the market to meet all of surgeons' requirements: high sensitivity, compactness, sterilizability, autonomy (wireless operation), manoeuvrability, user-friendliness, ergonomic design and option of real-time statistical data analysis," Eugène Grigoriev, a physicist and CEO of Forimtech, told *Medical Device Daily*.

FROM NUCLEAR PHYSICS TO MEDICAL PHYSICS

Grigoriev is the scientific advisor to the Director of the Institute for Theoretical and Experimental Physics at the Kurchatov Institute (National Research Center in Moscow, Russia). He has been working on multi-channel systems for particle detection at the European Organization for Nuclear Research (CERN) in Geneva, Switzerland since 1975. The current technology was developed as part of the Medtech Project at the Swiss Commission for Technology and Innovation, in collaboration with the Swiss Federal Institute of Technology in Lausanne and the nuclear medicine and visceral surgery departments at Lausanne University Hospital (CHUV). New- generation Radpointer probes for radio-guided surgery are protected by several patents, in particular an American patent titled "A method and device for detecting, localizing and analysing a radioactive source in material, e.g. biological tissue," obtained in 2013.

The system consists of a simple pen-sized, compact probe using scintillators coupled to silicon photomultipliers to detect positron emissions or gamma rays directly. This single photon counting technique has sub-nanosecond timing, resulting in smaller, lighter, cheaper and more sensitive probes that are compact, easily sterilized and disposable. These features have opened up opportunities for intra-operative probe techniques to be used more widely.

The probe tip has a small window to detect gamma rays and positrons emitted by substances injected into patients. A scintillator converts gamma-ray energy into photons, which are in turn detected by an ultra-sensitive sensor. Most functions (signal analysis, detection controls and visual/audio user interfaces) have been moved from the probe to an external PC with pre-installed proprietary software, which is wirelessly connected to the probe. This platform can therefore be installed on any PC, communicating with it via Bluetooth within a 10 m range. The analysis results are given as a ``Geiger-counter`` sound and a number displayed on the computer screen: the closer the probe comes to a tumor, the higher frequency of the sound and higher the on-screen number.

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REGULATORY FRONT

While U.S. government-supported clinical trials of Zika vaccines are progressing, the damage caused by a delay in funding will continue to hurt other programs, **Health and Human Services** (HHS) Secretary Sylvia Burwell said Monday in a media call to discuss progress in the battle against the mosquito-borne virus. While waiting for Congress to supply emergency funding, HHS agencies borrowed resources from other programs and spent a lot of time and energy in finding funding rather than working on solutions, she noted. Assistant Secretary for Preparedness and Response Nicole Lurie said her agency, which includes **BARDA**, is behind where it should be in developing Zika vaccines and diagnostics and has seen manufacturers walk away from the space because of the uncertainty. Anthony Fauci, director of the **NIH's** National Institute of Allergy and Infectious Diseases, said NIH had to take money from efforts to fight malaria, Ebola and other diseases to continue work on Zika. "None of that money is going to come back to us," he said, noting that the first Zika vaccine trial is ahead of schedule but at "significant cost" to the other programs. Nine vaccines, using different technologies, are in development, according to Lurie, who pointed out that it typically takes five to nine starts to get one vaccine across the finish line. As of Sept. 28, more than 25,000 cases of Zika infection had been reported in the U.S. and its territories. Of those, 3,600 cases were reported in the 50 states, Burwell said.

Glaxosmithkline plc (GSK), of London, agreed Friday to pay $20 million in civil penalties to resolve U.S. **SEC** charges of Foreign Corrupt Practices Act (FCPA) violations. The charges stem from a scandal in China, in which company sales reps were accused of bribing doctors and hospitals, from 2010 through June 2013, to use GSK drugs to increase their sales bonuses. As part of the settlement, GSK also agreed to periodically report to the SEC on the status of its FCPA compliance and remediation efforts. The SEC penalty comes on top of court action in China that included a $490 million fine for the company and suspended prison sentences for a few GSK executives.

The U.S. **Patent and Trademark Office** (USPTO) issued a proposed rule that would hike several patent fees, which were last set in March 2013. For instance, the large entity utility filing, search and examination fee rates would increase to $300, $660 and $760, respectively, representing increases of $20 to $60. Small and micro entity discounts would be available. Bigger fee spikes are proposed for reviews before the Patent and Trademark Appeal Board (PTAB) to better align the fees with PTAB costs. Under the proposed rule, the fee for requesting an inter partes review of up to 20 claims would be $14,000, an increase of $5,000. The fee for requesting a post-grant or covered business method review involving up to 20 claims would be $16,000, or a $4,000 increase. The USPTO is seeking comments on the proposed rule.

Nobel

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continuation to a phase II trial, however it is too early for patients to seek treatment outside the setting of a clinical trial." A phase II trial is being planned currently in the planning stages.

There is preclinical evidence, in neuronal cultures and mouse model, for a number of drugs as autophagy boosters that could be useful for treating both age-related neurodegenerative disorders and those that are due to inborn errors of metabolism. Those drugs include antihypertensive drug Covera-HS (verapamil), Catapres (clonidine), which is both an antihypertensive and a sedative, and multiple others.

It is worth noting, though, that boosting autophagy is unlikely to be a slam-dunk. A 2016 review in the journal *Brain* included Dimebon (latrepirdine, Medivation Inc.), in a table of "modulators of autophagy in neuronal disease models".

To date, though, that preclinical promise has not shown up in clinical trials. Dimebon's development was discontinued in 2012 after the drug had failed to meet its endpoints in three separate trials for Alzheimer's and Huntington's disease.

Like many discoveries with truly broad implications, Ohsumi's research into autophagy was driven primarily by intellectual curiosity – hence his warning that it is not easy to know in advance which research will be useful.

In his 2012 interview after winning the Kyoto Prize, Ohsumi said that despite the current drive towards research that is explicitly translational, "you can answer the most basic and important questions about the nature of life through yeasts. My research was able to explain autophagy precisely because I was working on yeasts and could observe them under an electron microscope." //

Forimtech

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COMPACT, WIRELESS PROBE PERFORMANCE

Formintech has developed two probes. The first – Radpointer-Gamma – weighs 100 g and has a positron energy range of 50-250 kiloelectronvolts (keV). This device is primarily intended for use in combination with single-photon emission computed tomography to locate and extract tumors or sentinel lymph nodes measuring 6 mm or more. The sensing tip contains a tungsten collimator inside stainless steel tubing to eliminate scattered background.

"The second probe – Radpointer-Beta – has a positron energy range of 100-2000 keV. This device is primarily intended for use in combination with positron emission tomography to locate minute quantities of cancerous cells measuring down to 3 mm and determine resection margins. This probe – weighing 70 g and measuring 20 cm long – is only sensitive to positrons, which have a very short range in tissue (0.5-5 mm, depending on the type of positron-emitting isotope). The probe therefore has a very thin, relatively fragile entrance window.

Both probes have been CE marked since 2015 and are being tested at CHUV as well as in French and Italian hospitals. "These probes have enabled us to locate tumors very accurately, even during operations. Minute, deep endocrine tumors are very difficult to see on PET and SPECT images," said Professor John Prior – head of CHUV's nuclear medicine and molecular imaging department – and Maurice Matter and Professor Nicolas Demartines of CHUV's visceral surgery department. This new-generation probe has a sensitivity of 60,000 counts per second per megabecquerel, i.e. is three to four times more sensitive than similar devices on the market. "As a result, patients can be injected with three to four times lower isotope activities, which would reduce both the cost and irradiation doses proportionally, said Grigoriev.

BIG POTENTIAL MARKET

There is a bright future for Forimtech, which was one of the 3 companies nominated to the 2016 CTI Swiss Medtech Award. This market has big potential since 80 percent of newly diagnosed cancer patients – 15 million people a year worldwide – undergo surgery. Advances in early-stage cancer diagnostics have created a growing need for such tools since small tumors and lymph nodes are not usually palpable and cannot be visually discriminated. "The only way to locate such objects is by using intra-operative probes, which provide higher spatial resolution than diagnostic scanners," said Grigoriev.

The existing global market for radio-guided surgical probes, which is very far from being fully explored, is estimated to be 841,600 probes a year, including 1,600 in Switzerland, 100,000 in the EU, 70,000 in the U.S. and Canada, 600,000 in BRIC countries (Brazil, Russia, India and China) and 70,000 in Latin America excluding Brazil. Forimtech eventually intends to capture 5-10 percent of this global market.

The company began marketing Radpointer-Gamma in Switzerland and the EU, and will be entering the BRIC, U.S., Canadian and Latin American markets within the next 5 years. "We're currently looking for investors to raise 8-10 million dollars of funds," said Grigoriev. //

Bernard Banga is head of MD Report press bureau (Paris).

REGULATORY FRONT

Biopharma and biotech advances swept the **USPTO's** Patents for Humanity awards this year. The four awards went to the **FDA** for developing an improved meningitis vaccine production process that's been used to immunize 235 million people in high-risk countries in Africa; **Case Western Reserve University** for creating a low-cost, accurate malaria detection device; **Gestvision** for developing a quick, simple diagnostic test for preeclampsia for use in developing regions; and **Global Food Fund at Intellectual Ventures** for creating a passive cooler that can keep vaccines cold over 30 days and donating dozens of the units to the fight against Ebola and other relief efforts. Honorable mention went to two companies: Paris-based **Sanofi SA**, for researching new malaria drug candidates with shorter, simpler treatment regimens that can potentially counter growing drug resistance, and **Alere Inc.**, of Waltham, Mass., for developing diagnostic assays for rapid, early HIV diagnosis at the point of care in low-resource settings.

CARDIOLOGY EXTRA

Keeping you up to date on recent developments in cardiology

By Amanda Pedersen, Senior Staff Writer

SAVR still matters, investigator says

Transcatheter aortic valve replacement (TAVR) may be growing in popularity as the TAVR industry continues to study the technology in lower-risk patient groups and pursue expanded indications accordingly, but surgical aortic valve replacement (SAVR) still matters, and remains an important treatment option for patients with aortic valve disease, according to a cardiothoracic surgeon presenting data this week at the European Association for Cardio-Thoracic Surgery (EACTS) in Barcelona. One-year outcomes from Medtronic plc's Pericardial Surgical Aortic Replacement study, nicknamed the PERIGON trial, demonstrated how the advanced design elements of the company's Avalus pericardial aortic surgical valve contribute to positive performance and outcomes, according to Robert Klautz, the co-primary investigator of the PERIGON trial. "The value of this large, contemporary dataset is that it allows surgeons to better understand treatment for today's SAVR patients, as opposed to data from older studies that may not be as representative," said Klautz, who is also head of the department of cardiothoracic surgery at the Leiden University Medical Center in the Netherlands. Dublin, Ireland-based **Medtronic plc**, noted that the PERIGON trial is a single-arm, non-randomized, prospective study of about 1,300 patients from 40 sites across Europe, Canada, Japan and the U.S., but the cohort presented at EACTS included 270 patients who were analyzed at the one-year endpoint. The vast majority (91 percent) of patients were at low mortality risk for open heart surgery, about 8 percent were at intermediate risk, and less than 1 percent of the patients were considered high risk for surgery. At one year, all patients showed low rates of all-cause mortality (3.6 percent) and cardiac death (1.1 percent). The primary analysis demonstrated positive clinical outcomes at one year, with low linearized rates of thromboembolism (2.2 percent), endocarditis (1.0 percent), all paravalvular leaks (0.5 percent), all hemorrhages (3.7 percent), and major hemorrhages (2.7 percent). No thrombosis, hemolysis, severe paravalvular leaks or structural valve deterioration were observed at one year. Additionally, patients treated with the supra-annular design of the Avalus valve also experienced improved blood flow performance with mean aortic gradients improving from 42.3 mmHg at baseline to 12.6 mmHg at one year, Medtronic said. Additionally, nearly three-quarters of patients improved one or two New York Heart Association functional classes from baseline to one year across all valve sizes. Rhonda Robb, vice president and general manager of Medtronic's heart valve therapies business, said the Avalus valve was designed to help facilitate procedural ease of use while enabling the lifetime management of the patient. The device is not approved for the U.S. or European markets.

Non-enzymatic mechanism can predict statin response via blood

Plaxgen Inc., of Fremont, Calif., published research in *The American Journal of Cardiology* describing a new non-enzymatic mechanism that modulates particle formation, possibly through direct interaction between statins and cholesterol aggregates, to change particles distribution from low-density lipoproteins to high-density lipoproteins. According to Plaxgen, the discovery could help researchers better understand how statins induce desirable HDL particles formation. It could also be useful in predicting patient response rates to statins, the company said, and could help the company in the ongoing development of its Statres test, which is designed to match patients to statins via a blood test. Not only do patient responses differ to different statins, the company noted that between 5 percent and 20 percent of patients do not respond to statins at all. Alan Wu, a professor of laboratory medicine at the University of California, San Francisco and chief of the clinical chemistry laboratory at San Francisco General Hospital, said this is the first time research has shown there are non-enzymatic mechanisms involved that could have an impact on predicting statin efficacy. Wu, who also co-authored the study, said the prevailing view of the mechanism of action for statins until now has been associated to inhibition of HMG-CoA reductase, a key step in the formation of cholesterol. For the study, the researchers examined the effect of multiple commercially-available statins on low-density and high-density cholesterol particles in blood serum samples using Plaxagen's Plaque Array platform, which combines flow cytometry and particle-targeted proteomics to identify the makeup of plaque particles derived from serum.

Investigators 'Xplore' new bioabsorbable pulmonary valve in kids

Xeltis AG, of Zurich, Switzerland, said three pediatric patients have been implanted with the first heart valve designed to enable cardiovascular restoration. The children have been enrolled in the Xplore-I study of the company's bioabsorbable pulmonary heart valve, a multi-centered European feasibility trial of patients ages 2 through 21. The trial is designed to assess the survival rate of patients undergoing right ventricular outflow tract (RVOT) reconstruction at six months following implantation of the bioabsorbable heart valve. RVOT reconstruction is an open-heart surgery often involving pulmonary heart valve replacement. It is usually performed

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in children born with congenital heart defects. The first three trial implants were conducted at Gottsegen György Hungarian Institute of Cardiology's pediatric cardiac center in Budapest, Hungary and the University Children's Hospital in Krakow, Poland. So far the device is performing according to expectations and trial details will be presented this week at the EACTS meeting. "Reconstruction and replacement of diseased heart valves in children using patients' own tissue could help reduce the risk of complications and of re-interventions observed with animal and human donor implants," said Thierry Carrel, principal investigator of the Xplore-I study, and a professor of surgery at the Clinic for Cardiovascular Surgery, University Hospital Bern in Switzerland. "We are quite confident regarding this technology, since children from the precursor feasibility study on bioabsorbable blood vessels demonstrate excellent results over two years after implantation." The FDA has granted a humanitarian use device designation for the Xeltis pulmonary valve as a bioabsorbable pulmonary heart valve for the correction or reconstruction of RVOT in children.

Memory of a heart attack may be stored in our genes

Both heredity and environmental factors influence the risk of cardiovascular disease, according to researches at Uppsala University. Results of their study, published in the journal *Human Molecular Genetics*, suggest that the memory of a heart attack can be stored in our genes through epigenetic changes. Although we inherit our genes from our parents at birth, chemical modifications of DNA that turn genes off or on, called epigenetic changes, can occur over the course of our lifetime, and these changes can lead to the development of various diseases. In the study, the researchers examined epigenetic changes in people who have had a previous heart attack. Asa Johansson, a researcher at the Department of Immunology, Genetics and Pathology, who led the study, said that during a heart attack the body activates certain genes. "This mechanism protects the tissue during the acute phase of the disease, and restores the body after the heart attack," Johansson said. "It is therefore likely that it also occurs epigenetic changes associated a heart attack." The results of the study showed there are many epigenetic changes in individuals who had experienced a heart attack. Several of these changes are in genes that are linked to cardiovascular disease. However, it was not possible to determine whether these differences had contributed to the development of the disease, or if they live on as a memory of gene activation associated with the heart attack, the researchers noted. In the long run, however, Johansson said the results may highlight the importance of epigenetic changes in the clinical picture of a heart attack, which in turn may lead to better drugs and other treatments.