BioWorld MedTech

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Replaces suture technique

Amsel marks first clinical use of occluder device

By Katie Pfaff, Staff Writer

Amsel Medical Corp. reported the first-in-man use of its Amsel Occluder device (AOD) during complicated vascular surgeries to ligate or occlude, or tie up and block chosen vessels during the procedure. Clinical usage occurred at NYU's Langone Medical Center, and was successful in ligating and occluding the vessels with positive reaction and goal performance.

AOD is used with open general surgery on vessels or tubular structures between 2.0 millimeter and 7.0 millimeter when a metal ligating clip is specified. The device provides an additional step beyond

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Inside

Unique market opportunity

Aethlon Medical eyes path to market via legacy EAP for Hemopurifier system

By Mark McCarty, Regulatory Editor

The 2015 expedited access pathway (EAP) for medical devices was revised by the 21st Century Cures Act, but Aethlon Medical Inc. of San Diego has wrapped up a feasibility study for its Hemopurifier device thanks to the legacy EAP program. Aethlon's CEO, Jim Joyce, told *BioWorld MedTech* that this device presented a few unique challenges for both the sponsor and the FDA, but that the number of untreatable pathogens – and the ease with which those pathogens travel

See Aethlon, page 4

Axonics initiates U.S. pivotal trial of sacral neuromodulation implant for overactive bladder

By Stacy Lawrence, Staff Writer

In an effort to best industry titan Medtronic plc, startup Axonics Modulation Technologies Inc. has started a pivotal trial for its implantable sacral neuromodulation system to treat urinary urgency incontinence. The Irvine, Calif.-based company expects its implant will have years longer battery life, and it is also much smaller than the device sold by Medtronic.

Axonics anticipates it could have the pivotal data in hand, followed closely by an FDA submission, during the third quarter of 2018. An FDA approval

See Axonics, page 5

Alternative to allogeneic transfusion

I-Sep's autotransfuser recovers red blood cells and platelets

By Bernard Banga, Staff Writer

PARIS – I-Sep SAS, a Nantes, France-based startup specializing in autotransfusion solutions for operating rooms, raised $1.44 million to speed up development of new autotransfusion technology for use during operations.

"This latest-generation autotransfuser will improve the quality of blood transfusions and extend access to autotransfusion during hospital operations," Sylvain Picot, CEO of I-Sep, told *BioWorld MedTech*.

Autotransfusion is an alternative to allogeneic transfusion, where blood comes from donors. Very

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The Undead

Molecular map may hold key to new cancer treatments

By John Fox, Staff Writer

The first 3-D map has been produced of the scaffold of a molecule called SgK223, which is now known to play a critical role in the development and spread of aggressive breast, colon and pancreatic cancers.

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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

Clinical trial technology firm, **Bracket**, of Wayne, Pa., reported the appointment of Christopher Crucitti as CCO and part of the global executive team. He brings experience in leading commercial efforts in R&D and clinical services, and will head global commercial strategy and development of Bracket's electronic clinical outcomes assessments and patient engagement platform, randomization and trial supply management, rater training and quality assurance, and the expanding mobile suite for patient diary and analytics.

San Diego-based **Illumina Inc.** reported Gary Guthart will join the company's board in December. Guthart is currently president and CEO of Intuitive Surgical, robotic-assisted minimally invasive surgery company, and served on the board at Affymetrix Inc. until its acquisition by Thermo Fisher Scientific Inc.

Richardson, Texas-based **Stephens & Associates**, a CRO servicing dermatology, cosmetics, medical devices and personal care firms, appointed Mark Dahl and Lawrence Rheins to head the newly opened Phoenix research facility. Dahl, medical director, is professor emeritus and former chairman of the department of dermatology at Mayo Clinic College of Medicine, Mayo Clinic Arizona, and the University of Minnesota Medical School. Rheins, senior director, has more than 30 years of experience in skin science and has served in various executive roles.

Medite Cancer Diagnostics Inc., of Orlando, Fla., developer of molecular biomarkers and medical devices for detection, risk assessment and diagnosis of cancer and precancerous conditions, appointed Austin Lewis as chairman and Stephen Von Rump as CEO, effective immediately. David Patterson, former CEO and chairman has retired. Lewis will continue as director, and Von Rump will transition from his prior role as chief commercialization and strategy officer.

Daily M&A

Mesa Laboratories Inc., of Lakewood, Colo., reported acquisition of substantially all of the assets and certain liabilities of **Bag Health Care GmbH**'s Hygiene Monitoring business. Mesa purchased only the Hygiene Monitoring business from Lich, Germany-based Bag and as a result, the sale and service of their other business divisions will continue as normal and are not affected in any way by the acquisition of the Hygiene Monitoring business.

Financings

Arqule Inc., of Burlington, Mass., closed a private placement with institutional investors led by the Pontifax Group pursuant to which the company raised gross proceeds of $9.5 million through the sale of about 8,370 shares of series A convertible preferred stock and warrants covering 2,260 shares of series A preferred. Each share of series A preferred together with the associated warrant is priced at $1,135 and will automatically convert into 1,000 shares of common stock upon the adoption of an amendment to the company's restated certificate of incorporation.

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Amsel

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ligation clipping by closing the chosen vessel and affixing it with a force similar to suture ligature, according to the company. AOD's secure placement is designed to eliminate slipping or loosening while in use, and can effectively replace suturing in areas that cannot be reached for that procedure.

Gold standard suture

The NYU procedures included "complicated vascular procedures" with target areas in need of occlusion, Bill Edelman, chairman of the board, Amsel Medical, told *BioWorld MedTech*.

"[AOD] duplicates a gold standard method of closing a vessel, which is called a transfixion ligation suture. That's a technique surgeons have practiced for decades," he said. "[AOD] allows you to perform that technique, the gold standard of vessel closure, by using this device anywhere in the body that you can reach."

Amsel's device can add greater access to veins or arteries in need of occlusion. Those that would otherwise be inaccessible for suturing due to the location in the body can be occluded with the device.

"The [transfixion ligation] suture technique is the standard suture technique taught to surgeons, the problem with it is that you can't reach everywhere you want to do this," said Edelman. "But the device that Amsel has produced can allow you to effectively duplicate this method using these clips anywhere in the body that you can reach."

Vein and artery closure

Amsel's device can provide secure closure of veins or arteries when necessary in open surgery, and replaces the need for ligating clip or vessel suture. Using a proprietary mechanical configuration, AOD is able to clamp a vessel during surgery and close the vein or artery.

"The device operates by piercing through the vessel with an 18 gauge needle and then extruding above and below the vessel two opposing nitinol clips, which compress the vessel," said Edelman. "[The device] compresses in a manner that doesn't damage the tissue based upon how the force is distributed, so it's designed to be permanent but also not to compress the tissue to the point of damaging the tissue."

Research published in the March 2017 issue of the *Journal of Surgical Research* suggested positive results from a study of 20 arteries in 10 pigs with veins occluded by either the device or ligaclip. According to the study, "A novel secure transfixing blood vessel occluder: comparison with the hemoclip in the porcine model," the device was safely and easily used and less likely to become loose than clips.

The report concluded, "The [Amsel device] is simple to deploy and securely maintains occlusion by transfixing the targeted vessel, unlike the widely used, nontransfixing ligaclip, that has a tendency to dislodge. As such, the Amsel secure vessel occluder opens up numerous treatment opportunities in both the venous and arterial systems to minimize open, laparoscopic, robotic surgical and interventional procedures, and reduce patient morbidity and its associated health care costs."

> *"AOD duplicates a gold standard method of closing a vessel, which is called a transfixion ligation suture.*
>
> Bill Edelman
> Chairman of the board, Amsel Medical

Clearances and market launch

In September the firm received FDA 510(k) premarket notification for its low-profile AOD, and won premarket notification for AOD in February 2015. The device also will be showcased at the 2017 Veith Symposium Nov. 14-18 in New York. Amsel will continue to investigate additional applications as well as clearance in Europe, build its portfolio and plan future efforts to bring the device to market.

Though the Amsel device is intended to be used instead of the suture technique to close targeted veins, arteries or tube structures, occluder devices are used in other surgical procedures, such as atrial septal defect (ASD). St. Jude Medical LLC, of St. Paul, Minn., has a minimally invasive transcatheter ASD device, the Amplatzer septal occluder to close the defect with additional tissue growth. W. L. Gore & Associates, of Flagstaff, Ariz., also offers its catheter-delivered Gore Cardioform septal occluder to treat ASD or patent foramen ovale, with the minimally invasive device. The implanted wire frame promotes closing of the defect. ♦

Financings

Insulet Corp., of Billerica, Mass., has priced a private placement of $350 million principal amount of convertible senior notes due 2024. The size of the offering was increased from the previously announced $300 million principal amount due to strong investor demand. The notes will bear interest at an annual rate of 1.375 percent and will mature on Nov. 15, 2024, unless earlier converted, repurchased or redeemed. Insulet also granted the initial purchasers of the notes an option to purchase up to an additional $52.5 million principal amount of notes.

Microbot Medical Inc., of Hingham, Mass., has been awarded an additional non-dilutive grant of up to about $735,000 from the Israel Innovation Authority of Israel's Ministry of Economy. The grant provides additional sources to be utilized by the company for the continued development of the company's self-cleaning shunt for the treatment of hydrocephalus and normal pressure hydrocephalus.

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Aethlon

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between continents – makes the Hemopurifier a device with a unique market opportunity.

The Hemopurifier device is a single-use, disposable cartridge that is populated with thousands of fibers with pores of roughly 200 nanometers in diameter, and which has successfully demonstrated the ability to capture a variety of pathogens, including hepatitis C virus, Ebola, Zika and several strains of influenza.

The feasibility study was designed to enroll 10 dialysis patients with hepatitis C in the Houston area, but the advent of drug treatments for the disease made enrollment difficult, and the company presented the FDA with data from eight patients treated over a period of two years. However, the device is capable of filtering exosomes associated with tumors as well, suggesting that this device could have a much wider range of applications than just the pathogens that populate the world of communicable diseases.

Joyce said the Hemopurifier cartridge fits in-line with dialysis equipment, and while the recently completed study focused on dialysis patients with hepatitis C, "we also have a history of other studies of treating non-dialysis patients, but utilizing the dialysis instrumentation in bypass mode."

The 2-inch by 11-inch cartridge has about 2,800 fibers, through which blood flows at a rate of about 200 milliliters a minute. The fibers in the proximal one-third of the device exert a pressure differential that forces particles smaller than the median fiber pore size (about 200 nanometers, far smaller than red blood cells) into the extraluminal space between the fibers and the cartridge shell.

At this stage, a plant-derived affinity lectin, composed of agglutinin derived from the *Galanthus nivalis* (or snowflower), binds to the glycan structure on the surface of the target pathogen, thus isolating the pathogen. The more distal end of the fibers exert a reverse pressure, thus pulling along anything not captured by the fibers. Joyce said the need for non-drug treatments for pathogens is significant, pointing out that no viable treatment is available for 38 of the 42 category B and C priority pathogens designated as such by the National Institute of Allergy and Infectious Diseases.

No neat category

"A lot of these pathogens represent indications that would be considered orphan designations" for either humanitarian device exemptions or as biologics, Joyce said, but he said the Hemopurifier does not fit neatly into either category. The company is in talks with the FDA regarding what might be described as a hybrid orphan-EAP pathway for testing the device simultaneously on a range of viruses rather than the standard approach of one virus at a time.

Joyce said the company has run up against a cultural challenge from the early days of the Hemopurifier project. He said the company started working on the device shortly after passage of legislation that gave birth to Project Bioshield, adding, "at that time, the focus was on trying to align a single drug with each and every threat. Devices were precluded by definition" from Bioshield, he said, although anything with any potential commercial value was also looked at askance.

In the interim, managers at the Department of Health and Human Services have become more amenable to the use of devices, but HHS is also more interested in broad-spectrum approaches as well. Joyce said expectations for treatment of communicable diseases are much higher than for one of the cancers, even when the communicable disease carries a comparable mortality rate, another problem of culture that has proved somewhat resistant to change.

When asked what sort of scientific challenges the company encountered, Joyce said, "the one challenge we had early on was how we were going to quantify the performance of our device," particularly when treating for a short term of three to four hours. "There was a concern that the gold standard was a reduction in viral load, but those reductions are often measured over an extended period of time," he said.

Polymerase chain reaction testing counts viral RNA, which means viruses that are and are not infectious are all counted. "FDA acknowledged that short-term reductions in viral load could be a significant challenge based on traditional measurement techniques," Joyce said, adding that the agency suggested development of an assay that would allow elution of the biological fluid from the device, from which viruses could be drawn for measurement. "That assay has proven to be significantly important" for Hemopurifier development, he said.

The idea of isolation and removal of pathogens lends itself more readily to acute infection than to chronic infection, but Joyce said that does not mean the Hemopurifier is necessarily of no help where chronic or long-term infections are concerned. "We don't have an expectation that someone would deploy this device as a stand-alone unless someone becomes fully drug resistant," he said, although the Hemopurifier could be used as adjunctive treatment for a chronic infection. ♦

Axonics

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is, optimistically, anticipated toward the beginning of 2019.

In taking on Medtronic, Axonics likes to use the successful chronic pain neuromodulation company Nevro Corp. as a comparator. Nevro has successfully challenged Medtronic, as well as Boston Scientific Corp. and Abbott Laboratories, in this arena by decreasing side effects and improving efficacy through improved technology.

"This is a perfect environment for a company with a cool technology to enter. We don't have any significant barriers that would get in the way of us being able to execute. I think the best analogy is Nevro. It has shown that you can be very successful in competing, in their case, with three very large competitors. And that you could, in a very short period of time capture a measurable percentage of the market. We don't have three large competitors, we have only one," Axonics CEO Raymond Cohen told *BioWorld MedTech*.

He said that an IPO for Axonics is under consideration, making the Nevro comparison a purposeful one. Cohen added that it's a proven therapy that is reimbursed widely in the U.S. and Europe. To pull off an IPO amidst the current relative med-tech IPO drought, he anticipates that the company would need positive U.S. pivotal trial results in hand, alongside a beta launch in Europe. There were roughly $700 million worth of sacral neuromodulation products sold last year, noted Cohen.

Nevro had its IPO in November 2014, and has since rapidly ballooned into a $2.3 billion market cap company, a path that Axionics would surely be happy to follow. For its part, Axonics has raised a total of $94 million since March 2014, including a bumped-up $35 million series C round this summer slated to back this U.S. pivotal trial.

Technology defined

Regulators in Europe and Canada already gave a nod to the Axonics r-SNM system in 2016. Commercialization has been postponed as the company pursues the U.S. pivotal trial, but Cohen expects to execute a European beta launch next year.

The Axonics r-SNM system includes a miniaturized rechargeable implantable neurostimulator that is expected to last at least 15 years in the body. Medtronic's system, known as Interstim Therapy, requires routine surgical replacement roughly every four and a half years, a concern since these patients are typically in middle age. In addition to the actual implant, the system includes a clinician programer tablet, a patient remote control, a tined lead and a charger.

"The average person who benefits from this therapy is a female aged 57 years old. So, this is a big consideration if they live for another 20 years or so or more even. You can see how that would become a deterrent. So, that is the number one distinction between our products," said Cohen. "Secondly, we have a device that is 60 percent smaller than the Medtronic device, and for this patient population that's a consideration."

He added that Axonics has also focused on innovating the patient-facing elements of the system. Charging requires roughly one hour, every two weeks; Medtronic's system doesn't allow for recharging.

Axionics r-SNM system; Axonics Modulation Technologies Inc.

Axonics hopes to offer the first rechargeable version of a sacral neurostimulation device.

Trial endpoints

The pivotal trial is expected to be in 120 patients at 15 centers in the U.S. and Europe, with a primary endpoint of at least 50 percent reduction in symptoms. Cohen noted that patients typically see relief in as little as two weeks, but that the FDA wanted to see longer term benefits with a six-month trial. The comparison period will be to the patient baseline prior to treatment.

In a 51-patient European trial, 71 percent of patients responded to therapy with a 50 percent or greater reduction in incontinence. Urinary frequency was reduced in this group to eight or fewer voids per day, which is normal. At baseline, the average was 14.3 voids per day and 9.6 urinary incontinence episodes, or leaks, per day.

The median patient in that study was 52 years old, with 75 percent of trial participants being women. After six months, 94 percent of responders continued to respond. At that time point, 85 percent of incontinence patients experience symptom reduction by more than half, alongside 81 percent of urinary frequency.

The Europe and Canadian approvals are for a range of indications including overactive bladder, urinary urgency incontinence, urinary retention and fecal incontinence. But, the FDA has required a much more narrow indication to start with: urinary urgency incontinence. Axonics said it's in discussions with the agency on how best to expand that into the other indications after an initial approval. The implant has been found to be suitable for all these indications with the exact same sort of placement and stimulation.

Cohen said Axonics had already provided the FDA with about 25,000 pages of documentation to substantiate its claim for a 15-year implant life, which the FDA reviewed prior to signing off on the pivotal trial.

"It's not like we invented a new therapy. The fact of the matter is that there is an existing market, with about 85 percent of that in the U.S.," summed up Cohen. There is demand for sacral neuromodulation, and we have a product that has additional benefits in terms of the various different product features such as long life and smaller size. We've been out talking to clinicians around the world for some time now, and we have significant demand for our products." ♦

I-Sep

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popular with the medical community, autotransfusion spares patients any risk of blood donor-recipient incompatibility as well as contamination risks. Autotransfusion enables patients' blood to be recovered, processed, concentrated and retransfused during operations. This is a very useful technique during surgery that may cause heavy bleeding or even hemorrhaging in excess of 2 liters. Nevertheless, this practice, which is used during 300,000 operations a year in France, has its limitations. "The technique currently used by blood autotransfusers on the market washes blood via centrifugation to spin and concentrate red blood cells. This technology does not supply platelets needed for coagulation," said Picot. Massive hemorrhaging – more than half a patient's blood mass, i.e., 2-2.5 liters of blood loss – during operations requires a secondary infusion of platelets or else patients will have coagulation problems. "I-Sep's idea was to improve blood-transfusion quality by creating a specific filtration procedure that preserves platelets," said Picot.

I-Sep was set up just two years ago in Nantes by three associates: Sylvain Picot, a biochemical engineer; Bertrand Chastenet, a former manager and consultant in the pharmaceuticals industry; and Francis Gadrat, an anesthesiologist at Bordeaux University Hospital. I-Sep's new technology is the result of eight years' research by Gadrat on a membrane-separation method providing an alternative to centrifugation. During the course of his research, Gadrat studied separating blood components by cross-flow filtration. This filtration procedure separates particles in a liquid on the basis of their size. Liquid flows parallel to the filter, unlike with dead-end filtration where liquid flows perpendicular to the filter. The liquid's pressure causes it to pass through the filter, enabling fairly small particles to go through the filter while oversize particles continue their course in the flow.

"Our technology is protected by two patent families, which cover both adapting cross-flow filtration membranes to blood and the machine organizing how filters and other consumables in the system work," said Picot. Since I-Sep was established, its nine-strong team of doctors, biomedical and biochemical engineers, has been collaborating with the anesthesia/intensive care departments at Nantes, Bordeaux and Rennes University Hospitals, as well as with the French national blood service (EFS). "We've also worked on modeling blood-cell flow and configuring our filtration model with the interdisciplinary physics laboratory at the University of Grenoble and the chemical engineering laboratory at the University of Toulouse," said Picot.

> *"I-Sep is first and foremost targeting the French autotransfusion market to meet the needs of large hospitals and smaller health facilities. Our sights are also set on emerging countries, as well as on the European and global markets.*
>
> Sylvain Picot
> CEO, I-Sep

Blood transfusion during surgery; I-Sep

Quick assembly in operating rooms

This new autotransfuser will weigh 15-20 kilograms and is expected to have a small footprint (40 cm x 40 cm x 30 cm). According to Picot: "We've designed this equipment to be transportable and fit easily into racks attached to hanging units on operating room ceilings." Special attention has been paid to ergonomic design; the device is intuitive to use and has a simplified interface. "The simple interface runs like a smartphone and can be used by any nurse, even without specific training," said Picot. The device has just five controls and three operating modes: adult, pediatric, and an emergency program. The autotransfuser is assembled in less than 10 maneuvers, which, according to Picot, "will cut assembly time to four minutes, i.e., half the time required for current autotransfusers on the market."

After validating the proof-of-concept in 2016 and carrying out technical tests on a laboratory based experimental facility, I-Sep went ahead with clinical trials on mini pigs in 2017. These trials are being conducted on the experimental technical platform at Nantes-Atlantic National College of Veterinary Medicine, Food Science, and Engineering.

Challenger in a $300M global market

"Thanks to the second funding round that raised $1.44 million with the regional investor GO Capital and five business angels in the Nantes region, we're now making final technical adjustments and conducting the first clinical trials on animals. We're getting ready to launch a new funding round to raise $1-2.3 million. This money will enable us to carry out the first in-man clinical trial by the second half of 2018," said Picot, who

See I-Sep, page 8

SgK223

Continued from page 1

The Australian researchers who compiled the map are looking at ways of targeting parts of the molecular scaffold molecule that are critical for its function, thereby hopefully leading to novel strategies to target cancer.

The research arose from a longstanding collaboration between Walter and Eliza Hall Institute (WEHI) researchers Onisha Patel and Isabelle Lucet, and Roger Daly, a professor with the Biomedicine Discovery Institute at Monash University in Melbourne.

The researchers published their findings in the Oct. 27, 2017, online edition of *Nature Communications*.

Lucet, laboratory head of the Chemical Biology division at WEHI, said SgK223 belonged to a large family of pseudokinase enzymes, which have long been classified as being "dead enzymes," as they appear not to catalyze any biochemical processes.

"SgK223 lacks the critical residues that would allow it to function as a canonical kinase as such, so it is termed a 'dead' kinase or enzyme," she told *BioWorld MedTech*.

"Overexpression of SgK223 leads to enhanced cell migration, so high levels of SgK223 can jeopardize the proper functioning of the machinery that controls cell migration," Lucet explained.

"Because SgK223 doesn't have any apparent activity similar to other types of enzymes, it was largely ignored. However, in the past decade, we've come to realize that this 'dead enzyme' plays an important role in cell signaling," she said.

Among the pseudokinases, SgK223 is unique because it acts as a molecular scaffold, facilitating the assembly of vital signaling molecules, the activities of which control normal cell functions, including morphology and migration.

"Because of its primary role in facilitating assembly of signaling molecules, high levels of SgK223 can jeopardize normal cell functions and contribute to changes leading to cancer," Lucet said.

"High levels of SgK223 have been found in some aggressive subtypes of breast, colon and pancreatic cancers, suggesting it could be a target for novel anticancer therapies."

"SgK223 is overexpressed in . . . 74 percent of non-small-cell lung cancer patients, as determined using real-time polymerase chain reaction," Roger Daly, head of the Department of Biochemistry and Molecular Biology at Monash University, told *BioWorld MedTech*.

However, "the frequency [of SgK223 overexpression] is not known for other cancers," noted Daly.

"Dead enzymes, which are also known as catalytically inactive proteins, can play important regulatory roles, but to date have been largely understudied," he added.

Use of the Australian Synchrotron, the only such advanced type of particle accelerator generating X-rays in the country, enabled the researchers to obtain an unprecedented insight into SgK223's molecular structure.

"Because molecular scaffolds such as SgK223 are structurally large, we focused on a critical part of the protein and produced a 3-D map using facilities at the Australian Synchrotron [in Melbourne]," Onisha Patel, a senior postdoctoral fellow at WEHI, told *BioWorld MedTech*.

"With this map, we have now identified several regions of SgK223 that are essential for its ability to assemble signaling molecules," she added.

"Solving the 3-D map of SgK223 is a critical step in discovering how this molecular scaffold functions, and future research will verify whether targeting SgK223 could have an impact in treating cancers."

Daly said the availability of the new 3-D map of the SgK223 scaffold would enable researchers to investigate how targeting the molecule might impact cancer cells. "With this 3-D map, we can now start to look at how inhibiting SgK223 function by targeting particular regions of the scaffold affects cell growth and spread in cancers where it is present at high levels," he said.

"Defining the molecular map of SgK223 identifies specific regions of the protein amenable to targeting with small-molecule drugs that will block the function of SgK223," noted Daly.

"This may lead to the development of new treatments for difficult-to-treat cancers, including pancreatic cancer and triple-negative breast cancer.

"Our next step will be to define further the role of specific regions of SgK223, in order to identify optimal targets for drug development," said Daly. "Lucet's team is focusing on characterizing the structure and function of a related protein known as SgK269, which forms a complex with SgK223 and is also implicated in cancer progression." ♦

Other news to note

Accuref Diagnostics (ARD) reported its formation as a new division under **Applied Stemcell Inc.**, a Milpitas, Calif.-based provider of molecular and cellular reference standards for assay development, proficiency testing and quality control. The announcement comes as ARD continues to expand its product catalog to generate the largest panel of precision engineered reference standards on the market, with more than 215 CRISPR-engineered variants in its oncology catalog, and greater than 1,500 products.

Caris Life Sciences, an Irving, Texas-based developer of precision medicine technology, said it filed a patent infringement suit against **Foundation Medicine Inc.**, of Cambridge, Mass., in the U.S. District Court for the District of Massachusetts Boston Division. According to the complaint, Foundation Medicine infringes five U.S. Patents (Nos. 8,880,350; 9,372,193; 9,383,365; 9,092,392; and 9,292,660) held by Caris. The patents cover Caris' system of performing molecular profiling of tumors to identify treatment options. Caris is seeking damages and other relief for Foundation's willful infringement of Caris' patent rights by its Foundationone, Foundationact and Foundationone Heme products.

I-Sep

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plans to obtain CE marking and commercially launch I-Sep's autotransfuser in 2019.

This Nantes-based med-tech intends to occupy a unique position in the highly competitive autotransfusion sector. This market – worth an estimated $300 million a year – is shared by four key players: the leading U.S. firm Haemonetics Corp., Livanova plc, Fresenius SE & Co. KGaA and Medtronic plc. All these autotransfusion device manufacturers use the same technology: centrifugation.

According to Picot, the I-Sep "is first and foremost company targeting the French autotransfusion market to meet the needs of large hospitals and smaller health facilities. Our sights are also set on emerging countries, as well as on the European and global markets."

For now, Picot plans to capture 15 percent of the French market by positioning the price of I-Sep's device at half the cost of competing centrifugation autotransfusers, i.e., $8,700-11,600. I-Sep's global business model is based on selling consumables (filters, tubing and bags), which will sell for around $117 per kit. ♦

Other news to note

Cellsight Technologies Inc., of San Francisco, entered a collaboration with **Boehringer Ingelheim**, of Ingelheim am Rhein, Germany, to evaluate Cellsight's positron emission tomography imaging tracer, Visact, for future use in the development and monitoring of immune-oncological therapies. Visact ([18F]fluoro-arabinofuranosylguanine [18F]F-AraG), is preferentially taken up by activated T cells, thus, enabling the noninvasive determination of changes in T cell activation within tumor lesion(s) as a consequence of anticancer immune system activation. A clinical trial to evaluate immunological response to PD-1 checkpoint inhibition in squamous cell carcinoma of the head and neck is currently ongoing (NCT03129061).

Cerveau Technologies Inc., of Boston, reported an agreement with **Houston Methodist Hospital** to support multiple projects over the next several years. These research projects are for studies of an early stage imaging agent (MK-6240) to be used in positron emission tomography scans for assessing the status and progression of neurofibrillary tangles. As part of the agreement, Cerveau will contract with Houston Methodist to manufacture and supply the [18F]MK-6240 needed for the initiatives in the greater Houston area as well as support research initiatives at Houston Methodist.

Skyline Medical Inc., Eagan, Minn.-based producer of the FDA-approved Streamway system for automated, direct-to-drain medical fluid disposal, announced two proposed joint ventures with **Helomics Corp.**, of Pittsburgh, and **Cytobioscience**, of San Antonio, which are expected to diversify the company's business into the CRO services sector. The proposed joint venture with Helomics will leverage the Helomics D-chip platform to develop and market new approaches for personalized cancer diagnosis and care. Skyline will own 51 percent of the joint venture, with Helomics owning the remaining 49 percent. The proposed joint venture with Cytobioscience will provide Skyline with access to Cytobioscience's personalized research services. The merger agreement between Skyline and Cytobioscience that was announced Aug. 9, 2017, has been terminated in order to focus on structuring the proposed joint venture. The terms of the proposed joint venture will be announced at a later date.

Product briefs

Glytec LLC, of Waltham, Mass., reported results from a prospective quality improvement study led by Eastern Virginia Medical School were presented at the 17th Annual Diabetes Technology Meeting. The study observed that when providers used the Hospital-to-Home (H2H) module of Glytec's Eglycemic management system to guide insulin regimens prescribed at discharge, patients had no diabetes-related readmissions, urgent care visits or emergency department visits within the first 30 days. A total of 28 patients with diabetes were enrolled in the study. Insulin administered during hospitalization, whether intravenous and/or subcutaneous, was managed using the Glucommander module of Glytec's Eglycemic management system, an FDA-cleared software-as-a-service solution that provides personalized dosing recommendations and is integrated with the EMR. The average daily blood glucose among patients enrolled in the study was 152 mg/dL, a reduction of 71 mg/dL, or 32 percent, from the average admission blood glucose and well below mid-point of the goal range (140-180 mg/dL). After patients enrolled in the study were discharged, certified diabetes educators called them once every seven days for the first month to check on the status of their diabetes as well as their use of health care resources. Over this period, given the prescribed home insulin regimen guided by Glytec's H2H module, none of the patients had a readmission, urgent care visit or emergency department visit due to their diabetes or any glucose-related cause, and only one had an episode of severe hypoglycemia <40 mg/dL.

Second Sight Medical Products Inc., Sylmar, Calif.-based developer of implantable visual prosthetics that are intended to create an artificial form of useful vision to blind patients, said the U.S. **FDA** has granted Expedited Access Pathway designation for the Orion cortical visual prosthesis system. This designation is given to a few select medical devices in order to provide more effective treatment of life-threatening or irreversibly debilitating diseases or conditions.

Product briefs

Standigm Inc., a Seoul, South Korea-based company using artificial intelligence technology for drug discovery and development, launched its Expander and Hunter services at the 23rd annual Bio-Europe international partnering conference being held in Nov. 6-8, 2017 in Berlin. According to the company, the services provide customers a quick identification of a novel clinical use for their existing drugs and even potential drug candidates for specific diseases with low cost and effort. Standigm Expander discovers new indications for compounds, while Standigm Hunter discovers compound candidates that can be repositioned for a disease of interest.

Vaica Medical, of Tel Aviv, Israel, reported the launch of Capsuled, a personally customized medication adherence solution, supporting any medication modality, for the use of pharmaceutical companies. The device is designed to create an accessible gateway to all patient-related digital information, along with timed encouragement messaging. Vaica's technology will be immediately implemented in two extensive clinical studies conducted by one of the largest private hospital chains in Italy that chose to partner with Vaica and Telecare H24, a provider of telemedicine services. Patients with chronic diseases will participate in these studies that are aimed to improve medication adherence in patient populations characterized by suboptimal medication adherence.

Regulatory front

The **Central Drugs Standard Control Organization of India** announced a revised list of risk-based device categories, slotting a number of ablation devices into classes C and D, the latter of which is the highest risk group. CDSCO said radio-frequency ablation for cardiac arrhythmias will be deemed class D devices, while endometrial ablation via heat would qualify as a class C device. Bifurcation coronary artery stents would qualify as class C devices, while standard, straight-line stents and bioresorbable vascular scaffolds (BVS) devices would fall into class D. Angiography catheters will be class B devices, while embolic protection devices will be treated as class D products. CDSCO included nearly 250 device types in its new classification framework.

The U.K.'s **National Institute for Health and Care Excellence** (NICE) published a draft report on the use of the Senza spinal cord stimulation device by Nevro Corp. of Menlo Park, Calif., stating that the National Health Service should consider covering the device. NICE said the evidence for effectiveness for this treatment of neuropathic leg and back pain suffices to demonstrate better pain control than is available with low-frequency spinal cord stimulation, and that the Senza could save more than £500 a year, a net effect derived from the lower rate of complications and longer device durability. NICE will take comment on the draft assessment through Dec. 4, 2017. The Centers for Medicare & Medicaid Services recently terminated the new technology pass-through payment for the Senza in the outpatient final fee schedule for 2018.

Health Canada said it will reduce the amount of time needed to conduct inspections of device facilities under the Medical Device Single Audit Program (MDSA) by double-digit percentages for all manufacturers. The agency said companies with 15 or fewer employees would see audit times drop by 20 percent, while companies with between 16 and 45 employees would see their audit times fall by 10 percent. Surveillance and re-audit times for all manufacturers would fall by 20 percent as well. The agency reiterated that device makers that are not in compliance with the terms of the MDSAP by Jan. 1, 2019, could lose marketing license for their offerings.

Orthopedics Extra

Keeping you up to date on recent developments in orthopedics

By Holland Johnson, Executive Editor

Corin and Ossis complete joint venture agreement for customized hip, knee implants

Cirencester, U.K.-based Corin reported it has completed a joint venture agreement with Christchurch, New Zealand-based Ossis to offer the same technology for customized implants. Ossis has custom designed and manufactured titanium bone and joint implants, with more than 200 successful implantations around the world since 2007. Recently, Corin created a 3-D printing technology to manufacture its Trinity Plus, a revision hip acetabular solution. “With Corin’s portfolio we are able to provide personalized hip and knee solutions from bone-preserving primary implants to revisions,” Stefano Alfonsi, CEO of Corin, said. “Through this agreement we will extend our ability to support surgeons in the treatment of patients that require massive reconstruction. The objective is to combine the long experience of Ossis in custom-made implants with our connected information infrastructure to improve surgeons’ abilities to perform these life-changing procedures worldwide.” Corin said the joint venture with Ossis represents another important milestone for it in the creation of an interconnected network of technologies to provide solutions that maximizes value for patients, surgeons and health care providers.

Exercise alone, intervention combinations lower risk for injurious falls

Compared with usual care, exercise alone and various combinations of interventions were associated with lower risk for falls leading to injury, according to findings recently published in *JAMA*. “The key elements of an effective fall-prevention program remain unclear, which has hampered implementation of effective interventions,” Andrea Tricco, of the Li Ka Shing Knowledge Institute at Saint Michael’s Hospital in Toronto, and colleagues wrote. “Furthermore, a network meta-analysis ranking all available fall prevention interventions and their combinations has not been conducted.” Researchers conducted a systematic review of 283 randomized clinical trials with 159,910 participants. The mean age of the participants was 78.1 years, and 74 percent were women. The network meta--analysis included 54 randomized clinical trials and 41,596 participants. Interventions reviewed were vision, podiatry and multifactorial assessments and treatments; vitamin D supplementation; surgery; social engagement; quality improvement strategies; osteoporosis medications; floor modifications; exercise; environmental assessment and modification; electromagnetic field therapy and whole-body vibration; diet modification; devices; cognitive behavioral therapy; calcium supplementation; and basic falls risk assessment. Quality improvement strategies centered on increasing use of research in practice, and were classified at patient, clinic and clinician and health system levels, according to researchers. Primary outcomes were numbers of injurious falls and fall-related hospitalizations. Secondary outcomes were costs such as those related to the health care system, number of fallers, number of fall--related ED visits, number of fall-related physician visits, number of fractures, number of intervention-related harms such as muscle soreness from exercise, quality of life, and rates of falls. Potential comparators were exercise alone, intervention combinations lower risk for injurious falls calcium supplementation, vitamin D supplementation, combined clinic-level quality improvement strategies, multifactorial assessment and treatment. Tricco and colleagues found that with 97 percent likelihood, combined exercise and vision assessment and treatment appeared to be the most effective intervention to reduce injurious falls. The researchers found that pairwise meta-analyses for fall--related hospitalizations showed no significant link between combined clinic and patient level quality improvement strategies and multifactorial assessment and treatment relative to usual care. “Choice of fall prevention intervention may depend on patient and caregiver values and preferences. The results indicate the need for a tailored approach,” the researchers said. The article , published Nov. 7, 2017, is titled “Comparisons of interventions for preventing falls in older adults: a systematic review and meta-analysis.”

Long stoppage of bisphosphonates tied to more fractures

Older women taking bisphosphonate drugs for osteoporosis may want to be careful about stopping the drugs for long periods, as the risk of incurring bone fractures increases with the duration of the “drug holiday,” a researcher said. Analysis of more than 150,000 female Medicare beneficiaries identified through records as “highly adherent, long-term bisphosphonate users” showed that those stopping treatment for more than two years were 40 percent more like to develop hip fractures after adjustment for potential confounders, compared with otherwise similar women who stayed on the medications, said Jeffrey Curtis of the University of Alabama at Birmingham. Smaller but still statistically significant increases in hip fracture risk were apparent with shorter cessations of bisphosphonates, Curtis said during an oral presentation at the American College of Rheumatology annual meeting. A similar pattern was seen for wrist and distal forearm fractures, but the magnitudes were generally smaller and did not consistently reach statistical significance for durations of stoppage shorter than two years. However, Curtis stopped short of concluding that drug holidays should be avoided for older women on bisphosphonates. He noted that the absolute increase in

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Orthopedics Extra

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fracture risk associated with stoppages of two years or more was rather modest, about one extra fracture per 100 patient-years compared with women staying on bisphosphonates. He also pointed out that the drugs have risks of their own – such as osteonecrosis of the jaw with long-term therapy – that may be mitigated with holidays, and which were not addressed in the study. Curtis and his group drew on Medicare data from 2006 to 2014, seeking to identify women on long-term therapy including those stopping it for defined intervals. The researchers focused on those on continuous, highly adherent (at least 80 percent of prescribed doses) therapy for at least three years, at which time up to three years of follow-up for fractures began. Patients were excluded or censored if they were taking other bone therapies. The data analysis examined fracture rates associated with durations of drug cessation of zero to three months; three months to one year; one to two years; and two to three years. Although the highest fracture rates were associated with this last duration category, hip fracture risk was nearly as high for stoppages lasting less than three months. Curtis conceded that the Medicare data did not include specific reasons for stopping bisphosphonate therapy. Other limitations included the reliance on administrative data and the three-year limit on follow-up. Curtis said it would be useful to study effects of even longer cessations in bisphosphonate therapy.

Combined adequate vitamin K and D could improve knee OA

The combination of sufficient serum vitamin K and vitamin D status was associated with improved lower-extremity function in two knee osteoarthritis (KOA) cohorts, according to findings published online in *Arthritis Care & Research*. Having adequate serum levels of both nutrients was variously linked to better function, faster gait, and faster chair stand times at baseline and over time, suggesting that dual supplementation may benefit some KOA patients, whereas vitamin D supplements alone have not. While epidemiologic data have suggested that low vitamin D is associated with more radiographic OA and progression, most trials of KOA vitamin D supplementation alone have not shown improved structural or functional outcomes. Last year, for example, it was recently reported that vitamin D supplementation did not slow the rate of KOA joint space narrowing or produce reductions in pain, stiffness, and functional loss over a three-year period, leading the authors to conclude that vitamin D supplementation has no role in managing KOA. Randomized controlled clinical trials of co-supplementation might alter that view, said Kyla Shea of the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University in Boston, and colleagues. Using a single measurement, they evaluated baseline K and D sufficiency (as circulating phylloquinone/25-hydroxy vitamin D) and lower-extremity function in the Health, Aging Body Composition Knee OA Sub-study (Health ABC) cohort and then replicated the analysis in the Osteoarthritis Initiative (OAI). These two nutrients are mechanistically linked, because the expression of vitamin K-dependent proteins in joint tissues requires the 25(OH)D, active form of vitamin D. The 1,069 participants in Health ABC had a mean age of approximately 75, and more than 60 percent were female. Patients' function was based on the Short Physical Performance Battery (SPPB) and their usual 20-meter gait speed. Health ABC participants with sufficient plasma vitamin K (≥1.0 nmol/L) and serum 5(OH)D (≥50 nmol/ L) generally had better SPPB and Health ABC-PPB scores and faster 20-meter gait speed at baseline and over four to five years of follow-up . In the OAI analysis, sufficient combined intake correlated with overall faster usual gait speed and chair stand completion time over follow-up. The effect of higher combined nutrient status on lower-extremity function was additive, the team found. For example, in Health ABC those with circulating phylloquinone ≥1.0 nmol/L combined with 25(OH)D ≥50 nmol/L had, on average, a 0.04-0.07 meter per second (m/s) faster 20-meter gait speed (adjusted for confounders) than those with phylloquinone <1.0 nmol/L or 25(OH)D <50 nmol/L. In the Health ABC 400-meter walk test, circulating combined levels were not significantly associated either with completion time in those who completed the walk or with the ability to complete the walk at baseline. Analyzing each nutrient separately, the investigators also observed a slight positive difference in 20-meter gait speed. The difference in participants with < or ≥ 1.0 nmol/L plasma phylloquinone was 0.02-0.03 m/s (17), and the difference between participants with < or ≥ 50 nmol/L serum 25(OH)D was also, on average, 0.02-0.03 m/s. (A 0.05 m/s difference is considered clinically meaningful.) In the OAI cohort, sufficient combined K/D intake at baseline was associated with overall faster 20-meter gait speed, chair stand completion time, and 400-meter walk time among completers of the walk. The article was titled "Sufficient vitamin K status combined with sufficient vitamin D status is associated with better lower extremity function: a prospective analysis of two knee osteoarthritis cohorts," and it was published on Oct. 17, 2017.