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Iris transcatheter annuloplasty ring; Millipede Medical Inc.

Acquisition could add $450M to the pot

Boston Scientific doubles down on mitral valves with $90M investment, option to buy Millipede

By Omar Ford, Staff Writer

Boston Scientific Corp. is taking a deeper dive into the mitral valve space with a $90 million investment and an acquisition option agreement with Millipede Medical Inc. The Santa Rosa, Calif.-based company has developed the Iris transcatheter annuloplasty ring system for the treatment of severe mitral regurgitation.

Marlborough, Mass.-based Boston Scientific has the option to acquire the remaining shares of the company

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Inside

EVAR treatment for short aortic necks

Medtronic seeks new indication for Endurant with trial launch

By Katie Pfaff, Staff Writer

Medtronic plc will begin investigating its approved Endurant II/IIs stent system to build on existing clinical evidence for an additional approach with the Chevar endovascular aneurysm repair (EVAR) technique for abdominal aortic aneurysm (AAA) among patients with short aortic necks. Launched

See Medtronic, page 4

Lxrepair developing new generation of diagnostic tests for radiotherapy

By Bernard Banga, Staff Writer

PARIS – Lxrepair SAS, of Grenoble, France, is currently carrying out clinical trials on 300 patients from the Lucien Neuwirth Cancer Institute in the south of France.

One in two cancer patients is currently treated by

See Lxrepair, page 6

A $1B incentive could help antibiotic R&D investment, prevent resistance: EU study

By Nuala Moran, Staff Writer

LONDON – A €9.4 million (US$11.5 million) EU study investigating ways to invigorate antibiotic development recommends there should be a market entry award of $1 billion for companies that succeed in getting a novel product to market.

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Software workflow highlighted in FDA 3-D printing webinar

By Mark McCarty, Regulatory Editor

The FDA's final guidance dealing with technical considerations for additive manufacturing plowed little new regulatory terrain where the Quality Systems Regulations are concerned, but the agency's webinar on the guidance lent additional emphasis on software workflow, an element that will likely be examined closely during the agency's

See FDA, page 5

Machine learning speech analysis IDs youth at risk for developing psychosis

By Stacy Lawrence, Staff Writer

Artificial intelligence has the potential to analyze all sorts of human behavior, probably starting with speech, for anomalous patterns that indicate specific diagnoses or track disease progression. In a new paper published in *World Psychiatry*, researchers at Mount Sinai Health System and the University of California at Los Angeles have used machine learning-based speech analytics to predict psychosis onset in at-risk youth.

It was accurate at rates of 79 percent in a 34-patient cohort in New York City, and 72 percent in 59 Los Angeles patients. The researchers used

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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

Other news to note

Earlysense Inc., of Ramat Gan, Israel, reported new orders for the company's medical systems grew more than 400 percent in 2017 compared to 2016. Additionally, Earlysense almost tripled the number of beds being monitored at the end of 2017 compared to the total combined number of beds in the previous 12 years since the company's founding. Earlysense estimates that its installed systems helped global medical institutions collectively save more than $100 million in 2017.

Helius Medical Technologies Inc., of Newton, Pa., together with the U.S. Army Research Laboratory (ARL), has executed a Cooperative Research and Development Agreement establishing a platform for collaborative research programs. Subsequently, Helius and ARL executed a Joint Work Statement, launching a research program to investigate Helius' Portable Neuromodulation Stimulator for the enhancement of cognitive, emotional and physical readiness and response through mindfulness and meditation training.

Launchpad Medical LLC, of Lowell, Mass., said it has successfully used his Tetranite in animal testing to stabilize dental implants, and also for multiple orthopedic uses such as spinal fusion and bone fracture repair in the cranium and extremities. Launchpad Medical's new Tetranite biomaterial is the subject of a cell culture experiment – in space and on earth – with the results to compare any differences in key biomarkers linked to new bone generation. This experiment is studying the impact of Tetranite on bone generating cells called "osteoblasts" and how they produce new bone in a microgravity environment that simulates the conditions to cause osteoporosis.

Precision Nanosystems Inc., of Vancouver, is providing the Nanoassemblr technology as part of a collaboration with The Cancer Center at Beth Israel Deaconess Medical Center and the recently opened Non-Coding RNA Precision Diagnostics and Therapeutics Core Facility. This new facility is dedicated to the study of non-coding RNAs, which play an important role in regulating gene expression and are important for understanding, detecting, and treating disease.

Appointments and advancements

Pompano Beach, Fla.-based **Biostem Technologies Inc.**, a pharmaceuticals and regenerative medicine company, reported Jennie Sandqvist has joined the company's board of directors and audit committee. Sandqvist is a neurologist in Sweden, but maintains a residence in Ft. Lauderdale and has served as a shareholder and advisor to the company for more than a year.

St. Paul, Minn.-based **Cardiovascular Systems Inc.** an interventional peripheral and coronary artery disease treatment medical device company, appointed Rhonda Robb as COO. She will report to Scott Ward, CSI chairman, president and CEO. Robb brings experience in transcatheter and surgical valve businesses where she built teams, product portfolios, and worked to improve patient care.

CHF Solutions Inc., of Eden Prairie, Minn., appointed Vitaliy Epshteyn as vice president, operations and engineering. Epshteyn brings two decades of leadership, management, and engineering experience in the medical device and related industry. Epshteyn holds two U.S. patents for manufacturing methods and medical device development.

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Boston Scientific

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at any time prior to the completion of Millipede's first-in-human clinical study that meets certain parameters.

Upon the completion of the clinical study, Millipede has the option to compel Boston Scientific to acquire the remaining shares of the company. Each company's option period expires by the end of 2019.

Completion of this acquisition would result in an additional $325 million payment by Boston Scientific at closing with a further $125 million becoming payable upon achievement of a commercial milestone.

Millipede was founded in 2012 by majority investor Santé Ventures and Steve Bolling, and has been led by CEO and co-founder Randy Lashinski since 2014.

The Iris transcatheter annuloplasty ring is placed via a transfemoral venous approach. The femoral vein is accessed and a delivery catheter is advanced into the right atrium for tricuspid valve repair or to the left atrium through the fossa ovalis via a transseptal approach for mitral valve repair. The delivery catheter places the device supra-annularly and the ring is then anchored and cinched reducing annular size and valvular regurgitation.

"We expect transcatheter annuloplasty repair to be the most valuable tool for treating mitral regurgitation," Trish Backes, a spokesperson for Boston Scientific, told *BioWorld MedTech*. "We believe a complete ring annuloplasty repair approach as we see with Millipede's IRIS ring system will be the first line of intervention for many mitral regurgitation patients and will be used in an overwhelming majority of mitral repair procedures."

Boston Scientific estimates the transcatheter mitral repair plus replace market to be $1 billion by 2021 and approach $3 billion by 2025, with the majority comprised of repair procedures.

Boston Scientific on the rebound

This could be a step in the right direction for Boston Scientific, which stumbled late last year with a delay in the commercialization of its Lotus Valve, a device set to address the transcatheter aortic valve replacement (TAVR) market. (See *BioWorld MedTech*, Nov. 30, 2017.) Executives from Boston Scientific said they would address a timeline for the Lotus Edge valve, during the company's 4Q17 earnings call scheduled for Feb. 1.

Boston Scientific had to temporarily recall the first generation of the Lotus valve in Europe to investigate a locking mechanism issue. (See *BioWorld MedTech*, Feb. 24, 2017.) The problem was with a pin that connects the heart valve to the delivery system. In some instances, the pin released prematurely due to excess tension, the company said at the time. As problems mounted with the product, the company also delayed its PMA submission for the TAVR device.

Lotus was Boston Scientific's way of breaking up what some analysts have dubbed the TAVR "duoply" held by both Edwards Lifesciences Corp. and Medtronic plc, which both have approvals for valves in the U.S. and Europe.

Sean Lavin, an analyst with BTIG said the company could recover from the Lotus setbacks with its wide assortment of products.

"Boston Scientific's diverse products lower risk, strong management drives results, multiple new products and growth drivers are attractive, and margin expansion should insulate the bottom line," Lavin said.

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>
> Trish Backes
> Spokesperson, Boston Scientific

Mighty mitral market

Mitral regurgitation is caused by a leaking mitral valve, which then causes blood to regurgitate from the left ventricle to the left atrium of the heart. Over time, the condition can lead to or accelerate heart failure and heart rhythm problems. Many patients with severe mitral regurgitation have compromised heart function and are not able to tolerate open-heart surgery to repair or replace the leaking valve.

"This is an enormous market, with 4.1 million people with moderate to severe mitral regurgitation in the U.S. alone," said Joanne Wuensch, an analyst with BMO.

Irvine, Calif.-based competitor Edwards Lifesciences is in a 200-patient CE mark trial for its Cardiaq transcatheter mitral valve replacement (TMVR) device, which it acquired with the 2015 purchase of Cardiaq Valve Technologies Inc. for up to $400 million, with $50 million of that contingent upon a CE mark. (See *BioWorld MedTech*, July 13, 2015.)

Dublin-based Medtronic has now staked a claim to being the first company to start a U.S. pivotal trial in this field, adding to the prior advancements in transcatheter repairs of the mitral valve. (See *BioWorld MedTech*, Oct. 26, 2017.) The study will test the Intrepid TMVR system, which Medtronic gained from its 2015 acquisition of Twelve Inc. for $458 million. (See *BioWorld MedTech*, Aug. 26, 2015.)

In 2015, the TMVR space saw a flurry of M&A activity.

Abbott Laboratories reported plans to pay $225 million for the equity of Roseville, Minn.-based Tendyne Holdings Inc. that it did not already own, making the total deal worth $250 million plus potential regulatory-based milestone payments. (See *BioWorld MedTech*, July 31, 2015.) In a separate transaction, Abbott said it had invested in mitral valve repair company Cephea Valve Technologies Inc. with an option to buy. Financial terms of the Cephea transaction were not disclosed.

Richmond, British Columbia-based Neovasc Inc. is developing the Tiara Valve to compete in the space. The device does not yet have approval.

The now defunct TAVR specialist, Direct Flow Medical Inc. was working to get back into the mitral valve space. (See *BioWorld MedTech*, Jan. 15, 2016.) However, the Santa Rosa, Calif.-based company shut its doors when it failed to secure financing in December 2016. ♦

Medtronic

Continued from page 1

in Europe and Russia, the ENCHANT postmarket multicenter single-arm study will be the first real-world study to evaluate the Chevar technique with complex aneurysms with infrarenal necks greater than or equal to 2 mm, according to the company. Chevar employs a parallel graft chimney method, which combines an aortic graft stent and covered renal stents.

The non-interventional and non-randomized research, ENCHANT (ENdurant ChEVAR New Indication Trial), is planned to include 150 patients from 25 sites located in Europe and Russia. Primary endpoints will include safety evaluated by major adverse events up to 30 days post-index, and performance indicated by technical success at the index procedure, followed by lack of secondary intervention for 365 days.

Dublin-based Medtronic began enrollment at St. Franziskus Hospital in Munster, Germany with is principal investigator, Giovanni Torsello, professor and chief of vascular surgery.

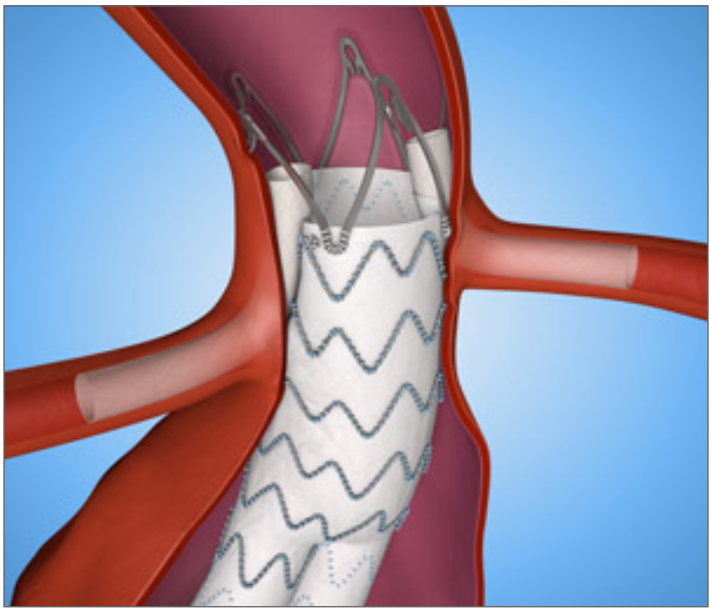
ENCHANT is hoped make the case for the chimney technique, and "build upon existing clinical evidence for the Chevar technique as a standardized approach for treating short infrarenal necks," said Torsello. "We believe the study marks another significant milestone for patients with complex forms of aortic disease who, until recently, had not been suitable for a minimally invasive endovascular procedure."

Endurant history in EVAR

Endurant II/IIs won CE mark for use with Chevar in December 2016, based on the PROTAGORAS study, which demonstrated impressive results among 128 patients. The combination technique and stent system demonstrated 100 percent technical success, significant aneurysm sac regression (p = .001), 95.7 percent primary patency of chimney grafts, and low occurrence of interventions, according to the company.

The original iteration of the Endurant system was awarded a CE mark in 2008 and FDA approval in 2010. Endurant II/IIs is currently approved in the U.S. for 10 mm or greater neck lengths and 60 degree or less infrarenal angulation.

While several stent systems are available to treat AAA, Medtronic claims the Endurant II/IIs and Chevar technique will be the first to treat patients with smaller-sized aortic necks, who would otherwise not be candidates for a minimally invasive surgery.



Endurant II/IIs; Medtronic plc. Note: The Chevar indication is not approved in the U.S.

"As the only stent graft company with a Chevar indication, we are deeply invested in delivering solutions, in partnership with the clinical community, that are backed by clinical rigor and address the unmet needs of AAA patients," said Daveen Chopra, vice president and general manager, aortic business in the aortic & peripheral vascular division, Medtronic. "This is the first industry-sponsored study to evaluate the Chevar technique in this patient population, and is another testament of our ongoing commitment to innovation in complex aortic disease and superior clinical outcomes."

> *"We believe the study marks another significant milestone for patients with complex forms of aortic disease who, until recently, had not been suitable for a minimally invasive endovascular procedure.*
>
> Giovanni Torsello
> St. Franziskus Hospital

Competition in short neck EVAR and AAA repair

Last spring, Irvine, Calif.-based Endologix Inc. launched its ELEVATE IDE clinical trial of the Ovation Alto abdominal stent graft system designed to repair infrarenal AAAs. The safety and efficacy study included 75 patients, and was intended to broaden the firm's reach in endovascular repair and complex AAAs. The study aim also was to treat patients with short aortic neck anatomy. (See *BioWorld MedTech*, April 3, 2017.) The Ovation portfolio, which received FDA approval in 2011, was acquired from the sale of Trivascular Technologies Inc., of Santa Rosa, Calif., for $211 million. (See *BioWorld MedTech*, Oct. 28, 2015.)

Shanghai-based Microport Scientific Corp. and Irvine, Calif.-based Lombard Medical Inc. began a strategic partnerhip in late 2016 with the former investing $15 million for exclusive marketing rights to Lombard's Aorfix and Altura stent graft systems for EVAR in Brazil and China. Aorfix was specifically designed to treat AAAs with difficult aortic neck angles, or up to 90 degrees, and received an FDA nod in 2015. (See *BioWorld MedTech*, Dec. 28, 2016.) Cook Medical and W.L. Gore Associates also offer EVAR devices. ♦

FDA

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review of premarket applications.

The FDA released the final guidance for technical considerations related to additive manufacturing in December 2017, a year and a half after the publication of the draft. This leapfrog guidance arrived with a statement by FDA commissioner Scott Gottlieb, highlighting the importance of the document, but the final lent little clarity over the regulatory distinctions between custom and patient-matched device manufacturing. (See *BioWorld MedTech*, Dec. 5, 2017.)

Matthew Di Prima, chair of the FDA's additive manufacturing working group, said software workflow "is critical" to design and production, a consideration he said captures style conversions and translations from digital file formats to the final printed form (the final guidance points to ISO/ASTM 52915:2016 for data file format considerations). Di Prima said aberrant workflow and the potential for human error could yield erroneous device design and/or software translation, and thus manufacturers will have to "analyze the workflow[s] for their effects on the additive manufacturing process."

Di Prima said the agency will want to see documentation of a "clearly described analysis to understand what these potential risks are and how they're being controlled." More to the point, he said, is information on how any variation in the workflow could affect the finished device. Device makers will have to ensure that variations in user accuracy do not affect device quality, and will have to document that they have examined the impact of each step in the workflow on the subsequent stages of workflow.

As for performance testing, Di Prima said worst-case scenario testing revolves in some part around the manufacturing technology and orientational location. Manufacturers should establish whether the margins of a device build space exhibit different mechanical performance properties than the more central areas of the device. The prospect that the manufacturing technology has an effect on material integrity should also be taken into account, and Di Prima said "the overarching concern with resorbable materials is that the additive manufacturing technology and processing doesn't change that resorption or degradation profile." ASTM F2924, a standard for 3-D printing of metals using powder bed fusion, was cited in this discussion.

Joel Anderson, a biomedical engineer at the Office of Device Evaluation, said complex device geometries makes removal of manufacturing residues a more complicated task, and thus, "we recommend . . . that you describe your manufacturing residue removal process and then validate the results." This process should take "the worst-case geometries" of the device, he said, and special attention might be paid to blind holes and areas that present the greatest porosity. Device placement in a sterilization chamber is of course part of the validation for cleaning or sterilization, but Anderson said any such procedures may have to include destructive testing of the device.

The agency will stick with ISO-10993 for demonstrations of biocompatibility, but Anderson advised that manufacturers will have to take into account the effects of photoinitiators and any other potentially toxic substances used in the process, "especially if using new materials with unknown long-term effects." ♦

Financings

Diabetes management company, **Glooko**, of Mountain View, Calif., and Gothenburg, Sweden, reported growth in the company's customer base of payers and health systems has provided momentum into the new year. The company has reached more than 1.5 million patients and 7,000 provider sites, including Fairview Hospitals, The University of Colorado and St. Luke's, and to primary care physicians offices where many type 2 diabetic patients are seen. Recent partnering with Ascensia's Contour Next One, and Dexcom G5 CGM (continous glucose monitor) has ramped up the firm's compatibility with the majority of insulin pumps, meters, and CGMs. Glooko has submitted its mobile insulin dosing system for FDA approval, which it hopes to receive by mid-2018. An additional $35 million was raised last year, led by Georgian Partners and including Insulet Corp., Mayo Clinic, Canaan Partners, Social Capital, Medtronic, and Samsung NEXT, which will be used to speed growth including internationally, and increase experience in data analytics.

Neuspera Medical Inc., a clinical stage, private venture capital-backed neuromodulation company based in San Jose, Calif., reported closing of its series B equity financing for $26 million led by Six Dimensions Capital, and all series A investors participating, including Action Potential Venture Capital and Windham Venture Partners. New investors were Delta Capital LLC and Purple Arch Ventures. Proceeds will be applied to product development and clinical programs for the company's implantable neuromodulation technology platform. Ching Zhu, a managing partner at Six Dimensions also joined the board of directors.

Lxrepair

Continued from page 1

radiotherapy each year, with about 3 million of those patients coming from Europe and the U.S. Some 5-8 percent of them develop hypersensitivity reactions (erythema, severe burns and inflammation), leading to treatment arrest. But there are no predictive markers for radiotherapy. Genetic predisposition affects DNA repair, with signaling pathways playing an important role in this hypersensitivity. Sylvie Sauvaigo founder and CEO of Lxrepair – and a former researcher at the French Alternative Energies and Atomic Energy Commission (CEA) – came up with the idea of identifying predictive biomarkers, based on the DNA repair-enzyme signature of isolated lymphocytes taken early during radiation therapy regimens. This enables such adverse hypersensitivity effects to be avoided.

"The trial will provide clinical proof-of-concept for Radx, our DNA repair characterization test to predict the toxicity of radiotherapy" Sauvaigo told *BioWorld MedTech*.

For the past 18 years, this biochemical engineer specializing in DNA repair has been working on methods to characterize all the DNA repair mechanisms. Most pharmaceutical laboratories use complex genomic and transcriptomic tools to sequence and characterize DNA mutations causing failure to anticancer treatments.

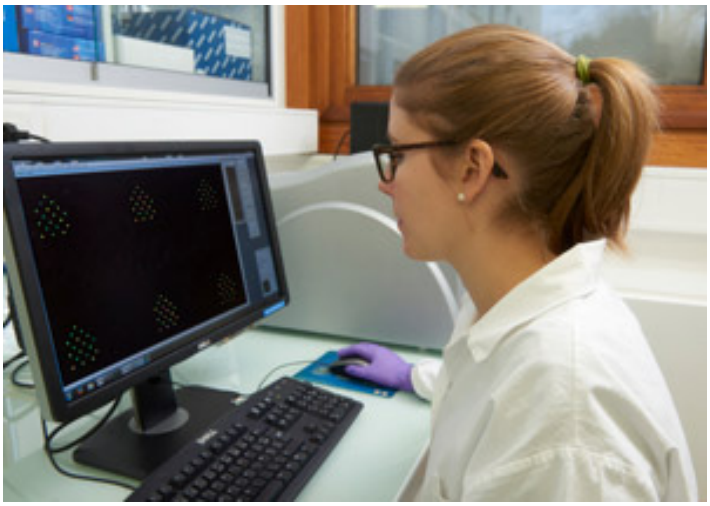
"We're the only company using a functional approach to characterize the entire DNA repair network, i.e., around a hundred proteins and enzymes," said Sauvaigo. This approach looks at how proteins and enzymes really function and identifies dysfunctional DNA repair pathways.

Lxrepair is a Grenoble-based startup, established as a spin-off from the CEA in 2013. The company develops a DNA repair biomarkers platform protected by three patent families. These patents cover processes for detecting and characterizing the activity of proteins that repair damaged DNA. Lxrepair's technology combines a multiplexed approach, enabling simultaneous screening of several enzymatic DNA repair activities from a single sample on a microsupport, and quantitative detection.

The four-strong team of chemists, radiobiologists and engineers in the company's R&D department has developed a DNA-functionalized biochip reproducing around 20 lesions caused by different DNA damaging agents. Protein extracts from the sample to be characterized are placed on the biochip, consisting of a glass plate. The plate has 24 tiles, each enabling around 20 determinations to be carried out on the protein extract. Lxrepair's Radx test uses a blood sample to identify (within a day) each sample's specific DNA repair signature, measured from fluorescent signals generated on the biochip.

"We expect to file a patent on a database of signatures for patients' response to radiotherapy treatment – with three classes of radiosensitivity – by the second half of 2018," said Sauvaigo.

In contrast to genetic tests, the functional aspect characterizes the real efficacy of various repair actions. "Multiplexing provides a wide range of information on the entire DNA repair network. These benefits make the Radx test especially



Lxrepair's DNA Repair analysis; Jean-Pierre Jayet

> *"Our enzyme tests based on measuring DNA repair establish patients' response to radiotherapy.*
>
> Sylvie Sauvaigo
> CEO, Lxrepair SAS

suitable for identifying defects causing therapeutic failure," said Sauvaigo. Radiotherapists should be able to predict which patients are likely to develop adverse effects, and hence lower radiation doses or choose other therapies: surgery or immunotherapy.

Since 2015, Lxrepair has been marketing – via the French company Bertin Pharma SAS (Montigny-le-Bretonneux, Yvelines) – the Glyco-spot kit. This is a multiplexed, fluorescent oligonucleotide cleavage assay, which simultaneously quantifies eight glycosylases and AP (apurinic/apyrimidinic) endonucelase activities for research use only.

Five months ago, Lxrepair raised $1.1 million to develop Radx, its promising diagnostic kit for radiotherapy. This funding was obtained from the French investment funds Kreaxi and Supernova Invest, Grenoble/Savoie/Mont-Blanc business angels, and a British fund – Xpand Investment – in the KIS Group. "Thanks to these funding rounds, we've entered 2018 demonstrating the clinical value of our test and reinforcing our patent portfolio," said Sauvaigo.

For the past 18 months, Lxrepair has been participating in the observational trial Radiation Impact on Thromboembolic Events (RIT), which aims to determine the frequency and identify the main risk factors for patients treated with curative intent by ionizing radiation. This trial to clinically validate Lxrepair's technology will be ending in a few months. It includes a cohort of 300 patients with solid cancer treated by radiotherapy or brachytherapy, from the Lucien Neuwirth

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Machine learning

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open-access, AI-based software that was developed by IBM to analyze speech patterns from transcripts of interviews based on existing manual linguistic analyses. The outcome of psychosis onset within two years after the interview transcripts were taken was known.

Screening for psychosis?

"We wish to improve prediction by using a technology that is portable, quick and easy to administer, requiring only a microphone. The computer software is a tool that can assist clinicians and researchers in psychiatry and other fields of medicine, in clinical assessment, as the computational assessment of language can index mental state, and content and patterns of thought," Cheryl Corcoran, associate professor of psychiatry and program leader in psychosis risk at the Icahn School of Medicine at Mount Sinai, explained to *BioWorld MedTech*.

She continued, "For psychosis prevention, we have excellent programs to evaluate and treat at-risk youths . . . But most individuals who develop psychosis have not had contact with any prevention program. Because speech is easy and inexpensive to capture and transcribe, and does not require any special equipment other than a microphone or a smart phone, which are ubiquitous, these analytic methods hold promise for identifying more individuals who may benefit from prevention strategies."

Ultimately, Corcoran envisions that this sort of approach could offer a useful, widespread screening tool among youth prior to the onset of psychosis, particularly for those patients who lack specialist access.

The software used is based on established manually coded linguistic analyses. Existing annotated manual transcripts were used to train the software to analyze semantic features (illogical thinking) and reduction in syntactic complexity (poverty of speech). The manual version has been used in previous research to predict psychosis onset with an accuracy of 71 percent, which is a substantial improvement upon a standard clinical assessment at only 35 percent.

So, the AI-based version based on the manual analyses actually improved upon it slightly. These sorts of manual assessments are quite time and resource intensive, and are largely available only through specialists at a handful of research centers. The AI analysis, however, could be applied much more broadly and routinely to boost efforts at early intervention.

Early treatment

Prevention or slowing of psychosis is difficult to achieve with existing approaches. Antipsychotic drugs haven't been shown to be particularly useful in the prevention of the onset of psychosis, which is characterized by a loss of touch with external reality. But Corcoran expects that early efforts at cognitive behavioral therapy could prove more useful.

"There's evidence to suggest that cognitive remediation can help improve cognition. It can at least improve function for individuals who are at-risk or who are already struggling a little bit. The hope is that with remediation, if we can improve cognition, maybe we could even prevent onset or at least help people function better when they do develop the illness. It's a kind of early interventions," said Corcoran.

> *"The hope is that with remediation, if we can improve cognition, maybe we could even prevent onset or at least help people function better when they do develop the illness. It's a kind of early interventions.*
>
> Cheryl Corcoran
> Icahn School of Medicine at Mount Sinai

Part of her research is focused on better understanding the underlying mechanisms that make speech pattern analytics useful in psychosis prediction. She expects not only that diminished language function is an indicator of eventual disease, but that the degeneration leading to these sorts of linguistic impairments may in fact play a part in triggering disease. So, if cognitive therapy can help to prevent the impairment of these linguistic functions, then perhaps it can offer a route to prevention or improved management for those prone to psychosis.

Research implications

Up next, Corcoran already is working on two federally funded studies to further extend this research in collaboration with IBM. One is focused on better understanding the underlying mechanisms in the brain circuitry during the progression into psychosis by examining high-risk youth with these speech analytics, alongside MRI and EEG data. The other will be a large study using the software analytics in hundreds of healthy and at-risk people globally that aims to better understand variation in progression to psychosis by factors such as age, gender, ethnicity and socioeconomic status.

In addition, she expects to further refine the technique used during these two studies. For example, determining if the 30 to 45 minutes of open-ended narrative used in the current study is the best format for data collection.

Transcript-based speech analytics also have obvious, inherent limitations, since they exclude voice inflection and facial expression. Corcoran anticipates that video-based analytics that address these aspects as well could be next, since a flat tone of voice and flat affect are common indicators of some neurological disorders.

Corcoran observed that AI-based speech analytics are being widely assessed to better understand and diagnose all sorts of neurological disorders, including dementia and Parkinson's disease. One study even analyzed distinctive kinds of speech patterns associated with specific illicit drugs, such

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AMR

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To qualify for an award, a product must meet a pre-defined target profile set by the World Health Organization and the company must agree to a stewardship program to avoid overuse that could prompt to the rapid development of bacterial resistance.

The final report of the project, Drive-AB (Driving reinvestment in R&D for antibiotics and advocating their responsible use) concluded that a $1 billion market entry award, given in annual installments of $200 million in the first five years after a product is approved, would significantly increase the number of new antibiotics coming to the market.

Rather than four antibiotics with distinct new mechanisms, as implied by current pipelines, there would be 16 to 20 "truly innovative" products over the next 30 years.

That is not a figure plucked from the air, but the finding of an extensive simulation based on a set of antibiotic-specific R&D and market parameters.

The $1 billion award would be in addition to sales of a product, a suggestion which some members of Drive-AB – involving 16 academic partners and seven pharma companies – argued would leave in place an incentive for manufacturers to oversell a product, promoting resistance. The consortium agreed that is a risk and said it must be monitored closely.

Drive-AB represents the most thorough piece of research to date into ways of fixing the economic model to incentivize companies to invest in development whilst promoting sustainable use of approved antibiotics.

Publication of Drive-AB's report coincided with the unveiling of the first independent comparison of pharma companies' current efforts to address antimicrobial resistance (AMR).

The benchmarking exercise, carried out by the Access to Medicine Foundation, concluded Glaxosmithkline plc and Johnson &Johnson Inc. lead the field in terms of investment in R&D and the size of their anti-infectives pipelines, and also in dismantling incentives for sales staff to oversell antibiotics.

There is a balancing act between making sure antibiotics are available when they are needed, particularly in developing countries, and ensuring they are not overused, said Jay Iyer, executive director of the Access to Medicine Foundation, launching the AMR Benchmark at the World Economic Forum in Davos, Switzerland, on Tuesday.

"It was a surprise to us; companies are taking action, for example changing the way they encourage sales, rewarding staff for their technical knowledge at a services level, so that antibiotics are not oversold," Iyer said.

The AMR Benchmarking study "highlights the challenges of developing these sorts of medicines," said Paul Stoffels, chief scientific officer of J&J, speaking at the launch in Davos.

As a specific example, Stoffels cited Sirturo (bedaquiline), J&J's treatment for multidrug-resistant tuberculosis. On its approval in 2012 – after eight years in development – it became the first new TB treatment in four decades.

But in order to preserve effectiveness, Sirturo has been strictly rationed to ensure only those whose infections will not respond to any other drugs get access.

The restrictions mean that to date only 40,000 patients have been treated with Sirturo. "It is absolutely not a viable business model," Stoffels said, adding, "But absolutely, from a human perspective, it was the right thing to do."

'A key turning point'

The Dutch and U.K. governments funded Amsterdam-based Access to Medicines to compile the AMR Benchmark. It parallels other indexes the foundation draws up to track the effort pharma companies put into ensuring their products are as widely available as possible.

The example of Sirturo underscores the need for new economic models such as those proposed by Drive-AB. The consortium, which was managed by the University of Geneva and Astrazeneca plc, assessed more than 30 incentive schemes in use in other industry sectors for how each would affect innovation, sustainable use and equitable access.

"Drive-AB's report is a key turning point in the global conversation about AMR," said John Rex, chief medical officer of the U.K. anti-infectives company F2G Ltd. and expert in residence at the medical research charity Wellcome Trust.

"[The report] provides global leaders with a vital roadmap for addressing the problem of AMR," Rex told *BioWorld MedTech*.

In addition to developing new economic models, Drive-AB has worked to define standards and metrics for tracking the responsible and appropriate use of antibiotics across different health care settings.

While market entry awards would represent a significant new approach to stimulating antibiotic innovation, traditional incentives, in the shape of nondilutive grant funding, also need to be boosted, Drive-AB said.

Currently, global public funding of antibiotic R&D stands at $550 million. That is too low, the report noted. "We estimate that $800 million is needed annually for [grant] funding." In particular, the estimated 400 SMEs that are involved in antibiotic R&D need more direct funding.

By itself, increased grant funding cannot fill the pipeline. "[It] pays for R&D costs but does not improve the attractiveness of the overall market," Drive-AB said. Without pull incentives in the form of market entry awards, "antibiotic-resistant infection risks becoming a neglected disease, solely dependent on public and philanthropic finance." ♦

Lxrepair

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Cancer Institute in Saint-Priest-en-Jarez. A blood sample is initially taken before patients' radiotherapy, followed by a second blood draw 24 hours after their first treatment session. In this way, the two signatures of patients' cells can be compared using the Radx test.

"It's more appropriate to compare the systemic response of each patient's body rather than carry out in vitro radiation," said Sauvaigo. The protocol is being coordinated by Professor Nicolas Magné of the clinical research and innovation department at the Lucien Neuwirth Cancer Institute.

Within the next two years, Lxrepair expects to obtain CE marking for its radiotoxicity marker on two indications: breast cancer radiotherapy (300,000 new cases/year) and prostate cancer (250,000 new cases/year) in Europe and the U.S. The company envisages a selling price of around $600 each for its radiotherapy kit. But it is not alone on the radiosensitivity rapid-tests market: Cvergenx Inc., DNAmito Inc., Exogen Biotechnology Inc., Novagray SAS and Neolys Diagnostics SAS have set their sights on a similar target.

Lxrepair has no intention of stopping at this potential market, worth $181 million for breast cancer and $151 million for prostate cancer. It is already conducting several other preclinical and clinical programs. One of these programs falls within chemotherapy and radiotherapy treatments for head and neck cancer (DNA Repair Enzyme Signature in Head and Neck Cancer with 120 participants, Lyon University Hospital), while the other (preclinical study) aims to discover new biomarkers and develop companion kits using its technology for targeted therapy of metastatic melanoma.

"Via these various applications, Lxrepair plans to enhance the value of its original functional repair-based platform. At the end of 2019, I intend to launch a $6 million-funding round to conquer the U.S. market," said Sauvaigo. ♦

Machine learning

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as methamphetamine or ecstasy, to enable determination of types of intoxication. For example, ecstasy users were found to have more relational and familial-oriented expressions that reflected connectedness.

Even beyond psychiatry, she pointed to analytics of early speech discrepancies as potentially useful in all sorts of disorders that involve mental state changes, such as diabetes and delirium.

Noted the paper, "Our finding of strong correlations between automated and manual linguistic variables provides evidence of concurrent validity for the natural language processing approach. Automated natural language processing methods are far more rapid and less expensive than manual linguistic approaches, and can be more readily adapted for research and ultimately in the clinic."

"Overall, we demonstrate the utility and validity of using automated natural language processing methods to characterize subtle disturbances in semantics and syntax across stages of psychotic disorder," the study concluded. ♦

Regulatory front

The U.S. **Senate** voted 55-43 Wednesday to make Alex Azar the next **Health and Human Services** (HHS) secretary. Seven Democrats joined Republicans in confirming the former Eli Lilly USA executive. While industry groups such as the Biotechnology Innovation Organization, Medical Device Manufacturers Association and Advanced Medical Technology Association were quick to congratulate Azar's confirmation, other groups were not happy about it. Prior to the vote, a coalition of health care, consumer and labor organizations delivered a petition with 300,000 signatures to Senate offices, demanding that the Senate investigate Azar's role in raising drug prices at Lilly and vote against his nomination, according to Public Citizen. Azar is President Donald Trump's second pick to lead HHS. Tom Price stepped down from the role in September amid criticism over his extensive use of private and military jets at taxpayers' expense. In comments on the Senate floor before the vote, Sen. Ron Wyden (D-Ore.), who led the opposition to Azar's nomination in the Senate Finance Committee, acknowledged that Azar didn't "carry the ethical baggage" of Price, but he went on to lambaste Azar for supporting Trump's health care policies. During the Finance Committee hearing earlier this month, former HHS Secretaries Tommy Thompson and Michael Leavitt, who both served under President George W. Bush, spoke glowingly of Azar's prior service at the department as general counsel and deputy secretary. They cited his work in responding to 9/11, the anthrax scare, Hurricane Katrina and a potential influenza pandemic while implementing the Medicare Part D program. Azar was confirmed for each of those HHS positions by a unanimous Senate.

Regulatory front

The **Provisional Accelerated Coverage to Encourage Research** (PACER) provisional coverage proposal is no longer on the docket at the U.S. Office of Management and Budget, seemingly bringing at least a temporary halt to a Medicare coverage mechanism that would bridge the gap between the coverage-with-evidence paradigm and the more typical Medicare coverage processes. The proposal, floated by the Medical Device Manufacturing Association, appeared on the OMB docket as the Expedited Coverage of Innovative Technology (ExCITe) proposal, where it was described as a pathway that "would remove the barrier in evidence generation by allowing CMS to provide faster access to new technologies that would have the potential to improve patient health and quality of care." MDMA President and CEO Mark Leahey said in comments to the docket for the 2018 Medicare physician fee schedule that PACER would call on CMS to deem any new technology approved by the FDA to be reasonable and necessary for a limited term to allow the sponsor to collect data in support of coverage. This mechanism could be administered by CMS and by Medicare administrative contractors, and Leahey said Medicare Advantage plans and private payers would likewise be encouraged to cover such devices.

The FDA's **Center for Devices and Radiological Health** said its strategic priorities for 2018-2020 include shifting from the center's role "from the traditional command-and-control gatekeeper to a true representative, participatory government entity that serves and enables rather than dictates to the public." Among the specific goals laid out for these next three years are to ensure that more than half of all novel medical technologies arrive in the U.S. market first or at least in tandem with other major markets by the end of calendar year 2020. That same date will serve as the deadline by which time the CDRH Engage Council will strive to achieve at least an 80 percent CDRH employee engagement, as is the case for an attempt to simplify at least 80 percent of the center's core processes. CDRH said it had exceeded its 2017 goal of gaining access to 100 million electronic patient records by 3 million as part of a push for the use of real-world evidence in support of regulatory decision-making, and nearly tripled rather than doubled the number of pre and postmarket decisions made at least in part on the basis of RWE. CDRH director Jeff Shuren said CDRH will unveil later this year a "Medical Device Safety Plan," which will go toward a focus on device features and manufacturing processes "that have the greatest impact on product quality and patient safety."

The **International Medical Device Regulators Forum** unveiled a draft guidance describing the essential principles for safety and performance for therapeutic and diagnostic devices. The scope of the draft covers both manufacture and device design, and spells out recommendations for risk management and clinical evaluation. The draft lists a number of existing international standards, including ISO 13485 for quality systems, and ISO 14971 for risk management, the latter of which is up for a rewrite by the International Organization for Standardization.

The U.S. **National Institutes of Health** said it will award $190 million over a period of six years toward development of genome editing technologies that can be applied toward patient care. The Somatic Cell Genome Editing program is designed to remove barriers "that slow the adoption of genome editing" for patient care, according to the NIH announcement, and entails development of assays to test the safety of gene editing technologies such as CRISPR/Cas9. NIH director Francis Collins said the focus of the program "is to dramatically accelerate the translation of these technologies to the clinic for treatment of as many genetic diseases as possible."

Aetna of Hartford, Conn., said it will cover the Heartware ventricular assist device by Heartware of Framingham, Mass., so as to "include the new FDA-approved indication" for destination therapy for advanced heart failure who are not eligible for transplant. The payer said it had previously covered the VAD for destination therapy only "when required due to the member's anatomy."

Product briefs

Cas Medical Systems Inc., Branford, Conn.-based provider of noninvasive cerebral oximetry patient monitoring devices, submitted a 510(k) application to the U.S. FDA for the Fore-Sight Tissue Oximetry OEM Module, an OEM version of its Fore-Sight Elite Tissue Oximeter. The OEM Module allows third-party manufacturers to incorporate Fore-Sight technology into their patient monitors as a solution for tissue and cerebral oximetry. The company expects to receive regulatory clearance for this product in 2Q18.

Cefaly Technology, of Seraing, Belgium, reported its Cefaly Acute, an external trigeminal nervestimulation device, performed successfully in a trial for migraine abortion. Previous pilot and pivotal trials (ACME) demonstrated the efficacy and safety of the Cefaly Acute and led to the FDA approval for the acute treatment of migraine with or without aura. The new trial on migraine abortion was identical to the design used to test abortive migraine medication, including medications already on the market (triptans) and the new drugs still under medical investigation: Lasmiditan, Ubrogepant and Rimegepant. The outcome at two hours of using Cefaly Acute showed that 70.8 percent of patients had pain relief, 35.4 percent were pain-free, and 60.4 percent were free from the most bothersome symptom (MBS). In comparison, available data on Lasmiditan shows 59 percent of patients had pain relief at two hours, 32.2 percent were pain free and 40.9 percent were MBS-free; for Ubrogepant pain relief at two hours was 58.8 percent, while 25.5 percent of patients were pain free; and for Rimegepant at two hours pain relief was at 61.2 percent, with 32.9 percent of patients pain free. At the 24-hour mark, sustained pain freedom with Cefaly Acute was 25 percent of patients. In contrast, Ubrogepant showed 21.6 percent, while Rimegepant demonstrated 28.2 percent. Based on these encouraging positive results Cefaly Technology is now moving forward with a phase III clinical trial in the U.S. that is scheduled to be completed by the end of the year.

Exalenz Bioscience Ltd., Modiin, Israel-based developer of noninvasive medical devices for diagnosing and monitoring gastrointestinal and liver diseases, said its Breathid platform, which is already commercially used as a standard of care test for *Helicobacter pylori*, showed positive clinical trial results in detecting clinically significant portal hypertension in non-alcoholic steatohepatitis (NASH) patients with compensated advanced chronic liver disease. Data from a total of 257 NASH patients who participated in two parallel studies comparing the use of the Breathid 13C-methacetin breath test (MBT) to invasive measurement of portal pressure demonstrate that MBT had high sensitivity and specificity in this patient population (88 percent and 85 percent respectively).

Livongo Health Inc., of Mountain View, Calif., reported that eligible members of the Livongo for Diabetes program will have access to the new Livongo for Hypertension program. In addition, Livongo will offer a stand-alone hypertension solution to new members. According to the company, Livongo is the first digital health company focused on managing both diabetes and high blood pressure. Using reinforcement learning, Livongo will offer real-time recommendations that are tailored to each person's health experience.

Mesa Biotech Inc., of San Diego, said it has obtained a CE mark for its Accula system, which can diagnose infectious diseases. The Accula system, a palm-sized, reusable dock with disposable test cassettes, offers the simplicity, convenience and procedural familiarity of traditional point-of-care rapid immunoassays, while providing the superior sensitivity, specificity and information content of laboratory-based polymerase chain reaction testing. Test results are available in approximately 30 minutes. The first available test in the EU market will be the company's Flu A/Flu B test, which is indicated for use with nasal swab collection that is less invasive than nasopharyngeal swabs and allows for a more comfortable specimen collection experience for the patient.

Rti Surgical Inc., of Alachua, Fla., reported the peer-reviewed publication of two-year data of the SImmetry sacroiliac joint fusion system in *The Open Orthopaedics Journal*. The data show SImmetry provides radiographically evident sacroiliac (SI) joint fusion as early as 12 months with higher fusion rates observed at 24 months, while effectively reducing pain in patients with SI joint disorders. This multisite study evaluated long-term fusion and pain reduction in 18 patients. The study examined computed tomography evidence of fusion at 12 and 24 months following SI joint fusion performed with decortication and bone grafting. At 24 months postsurgery, 17 of 18 patients (94 percent) had evidence of bridging bone, with 15 of 18 patients (83 percent) categorized as solid fusion across the SI joint. Of the patients with bridging bone, 15 of 17 (88 percent) were fused within the area of decortication, demonstrating the importance of this step in achieving fusion. No procedure- or device-related serious adverse events were reported.

Sebia SA, Lisses, France-based developer of multiple myeloma diagnostics testing and monitoring, received 510(k) clearance from the FDA for its Hydrashift 2/4 daratumumab assay, intended to be used with Hydragel IF, for the qualitative detection of monoclonal proteins in human serum by immunofixation electrophoresis. This in vitro diagnostic reagent mitigates the daratumumab-mediated interference seen in Immunofixation results for patients with multiple myeloma treated with Darzalex (daratumumab), a fully human monoclonal antibody that binds to CD38. The Hydrashift 2/4 daratumumab immunofixation assay is the result of a collaboration between Sebia and Janssen Biotech Inc., of Horsham, Pa.

Orthopedics Extra

Keeping you up to date on recent developments in orthopedics

By Holland Johnson, Executive Editor

New data increases concerns over MAGEC rod failure

Magnetically controlled growing rods have become a popular choice for treatment of early onset scoliosis, however, concerns have been raised over reports of metallosis, a type of metal poisoning, around failed MAGnetic Expansion Control (MAGEC) spinal growing rods, a type of magnetically controlled growing rods. A study, "Analyses of explanted magnetically controlled growing rods from seven UK spinal centers," which was published in the January 2018 issue of the journal *Spine,* analyzed explanted MAGEC rods to better understand why this is occurring. After analyzing 34 MAGEC rods from 18 children that were explanted for complications like failure of rod lengthening and maximum rod distraction reached, Thomas Joyce, professor of Orthopaedic Engineering, School of Engineering at Newcastle University in the U.K. and colleagues found that all 34 MAGEC rods had substantial titanium debris inside. In addition, 91 percent of the MAGEC rods showed measurable wear of the extending bar, towards the magnet end. In 74 percent of the rods, there was also damage to the radial bearing. And in 53 percent of the rods, O-ring seal failure was observed. Externally, all the rods showed "growth marks" on the extending bar component, which indicated the growth of the rod in vivo. The researchers wrote, "The combination of high volumes of titanium wear debris alongside O-ring seal damage likely accounts for the metallosis reported clinically around some MAGEC rods. Based on this explant data, a failure mechanism in MAGEC rods due to the natural off axis loading in the spine was proposed."

Study shows positive arthroscopic supraspinatus repair outcomes

New research from The Steadman Philippon Research Institute has found that arthroscopic rotator cuff repair can be ideal for patients with symptomatic partial thickness rotator cuff tears. The study, "Five-year outcomes after arthroscopic repair of partial-thickness supraspinatus tears," was published in the January 2018 edition of *Arthroscopy*. The authors wrote, "The study included 24 shoulders (24 patients, comprising nine women and 15 men). Follow-up data were available on 20 shoulders (seven women and 13 men, 83 percent follow-up) at a mean of 6 ± 1 years postoperatively. The mean age at index surgery was 55 ± 11 years; six bursal- and 14 articular-sided tears were repaired. No patient required revision surgery." The authors noted that the article highlights the outcomes at a minimum of five years after arthroscopic repair of partial thickness tears of the rotator cuff. "We were pleased to learn that the patients improved significantly after the surgery, with high satisfaction, low pain scores and low reoperation rates. We were also excited to learn that the improvements persisted over the course of the study." The most important findings were that the surgery effectively reduced pain and improved patient reported outcomes scores and that the results were durable over time with very low re-tear rates. It is worthwhile to consider arthroscopic rotator cuff repair in patients with symptomatic partial thickness rotator cuff tears, the authors said.

Scaffold-free MSC cartilage repair passes major test

The search goes on for a biologic solution to damaged or worn-down cartilage. Now a group of researchers at Osaka University in Japan have passed their first-in-man test of a novel, scaffold-free mesenchymal stem cells (MSC) solution. One year after implantation, healthy cartilage was present. What makes this approach so innovative is that is uses only allogenic MSC cells in a novel solution (supplier Twocells Company Ltd.) and then applies mechanical forces to "firm" up the solution into an injectable living cell treatment that will adhere to the knee and, without requiring a scaffold, differentiates and grows into cartilage repair tissue. The lead investigators at Osaka University have progressed to phase III in their clinical trial and this first-in-human test is highly encouraging. Importantly, this is a direct result of the stem cell bank at Osaka University's Medical Center for Translational Research. Researchers Norimasa Nakamura, Hideki Yoshikawa and Yoshiki Sawa tested this novel approach, which, in some ways, mimics nature's approach to driving progenitor cell differentiation. The Osaka team started with cell bank sourced MSCs, cultured them using a new form of cell culture solution, then, in a move that mirrors the natural forces, which signal progenitor cells to differentiate, applied mechanical forces to the culturing cells and created a scaffold-free, three-dimensional gel-like, injectable living tissue. As this first-in-human test demonstrated, the material can repair cartilage.

3-D cultures osteoblasts in peptide soup augur big changes in orthopedics

Working backwards, researchers have found that using calcitonin receptor fragment peptides (CRFP) with living cells in 3-D printed trabecular bone scaffolding could change the game in orthopedics. The study, "Biomechanical properties of 3D-printed bone scaffolds are improved by treatment with CRFP," appears in the Dec. 22, 2017, edition of the *Journal of Orthopaedic Surgery and Research*. The authors wrote, "3-D-printed scaffolds based on physiological trabecular bone patterning were printed. MC3T3 cells were cultured on these scaffolds in osteogenic media, with and without the addition of Calcitonin Receptor Fragment Peptide (CRFP) in order to assess bone formation on the surfaces of the scaffolds." The researchers noted that the lab is the first one to report that osteoblasts can be cultured on 3-D printing plastic scaffolds. The design of the experiment to seed stem cells and transform them into bone producing cells on artificial scaffolds is unique. They noted that reverse engineering to produce biomimetic scaffolds is the key to creating grafts and implants that are biocompatible. Also, discovering lead drug candidates like CRFP will enhance the anabolic drug portfolio in treating osteoporosis.