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AWAITING CVOT DATA

Pfizer halts its PCSK9 program as industry seeks clarity on class

By Marie Powers, News Editor

After advancing its proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, [bococizumab](#), into a global phase III development program that included six lipid-lowering and two cardiovascular (CVD) outcome trials (CVOTs), [Pfizer](#) Inc. blinked. The New York-based pharma said 52-week efficacy data showed “unanticipated attenuation” of low-density lipoprotein cholesterol (LDL-C) lowering over time along with a higher level of immunogenicity and a higher rate of injection-site reactions with bococizumab than with other agents in the class. Based on those findings,

[See Pfizer, page 3](#)

Turnstone's series B adds \$41M to advance trials of oncolytic viral immunotherapy

By Cormac Sheridan, Staff Writer

DUBLIN – [Turnstone Biologics](#) Inc. raised \$41.1 million in a series B round to accelerate clinical development of its next-generation oncolytic virus and cancer vaccine platform by deploying the technology in different combination

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IN THE CLINIC

BIOMARKER HOPE SPARKER

Upside 'on steroids'? NASH phase Ib winner for Durect; kidney damage bid up next

By Randy Osborne, Staff Writer

[Durect](#) Corp. CEO James Brown told *BioWorld Today* that, although phase Ib results proved encouraging with the

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THE BIOWORLD BIOME

THE GOOD MOUNTAIN AIR

Hypoxia has heartening results after myocardial infarct episode

By Anette Breindl, Senior Science Editor

According to the American Heart Association's website, “your heart muscle needs oxygen to survive. A heart attack occurs when the blood flow that

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NEWCO NEWS

Gigagen interrogates cells by the millions seeking therapies that mimic immune system

By Marie Powers, News Editor

[Gigagen](#) Inc. is a small company seeking to harness the power of genetic material, as its name implies, by the millions.

The 5-year-old company is the brainchild of David Johnson, co-founder and CEO, an inventor and entrepreneur who was among the founding members and served as chief operating officer of Silicon Valley genomics startup Natera Inc. Prior to Natera, Johnson served as project director of ENCODE, or Encyclopedia of DNA Elements, at the Stanford Human Genome Center.

Gigagen's other co-founder, Everett Meyer, who serves as the company's medical adviser, is assistant professor of medicine at Stanford University Medical School, where he specializes in immune profiling and immunotherapeutics.

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AUSTRALIA

Post IPO, Noxopharm heading to clinic with lead candidate idronoxil

By Tamra Sami, Staff Writer

PERTH, Australia – After completing its IPO in July, Sydney-based [Noxopharm](#) Pty Ltd. expects to have the first three clinical trials of its lead compound up and running in the first quarter of 2017.

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REGULATORY FRONT

The **Washington Legal Foundation (WLF)** and the **National Association of Manufacturers** filed an amicus brief asking the **U.S. Court of Appeals for the Third Circuit** to shut down repeat “bites at the apple” from states that choose not to opt out of federal class-action suits. The brief, filed in conjunction with *Glaxosmithkline LLC (GSK) v. the State of Louisiana*, noted that Louisiana did not opt out of a federal class-action suit based on claims that GSK tried to delay approval of generic versions of its allergy relief drug Flonase (fluticasone propionate). When the settlement was finalized in 2013, Louisiana sought and received \$183,000 as its share of the settlement. A year later, Louisiana – represented by private counsel on a contingency basis – filed a nearly identical suit in state court, seeking additional damages, the WLF said. The federal district court that approved the settlement refused to enjoin the state suit, saying that Louisiana was entitled to Eleventh Amendment sovereign immunity, which precludes it from being made a party to a federal court action without its “unequivocal consent.”

Although the U.S. government has been somewhat dismissive of a report put out in September by the **UN High-Level Panel on Access to Medicines** because of its narrow focus on patents as the barrier to access to drugs and devices across the world, Brazil, China, India and South Africa have asked that the **World Trade Organization** add the report to the agenda for next week’s session of the Council for Trade-Related Aspects of Intellectual Property Rights. U.S. officials have said the panel’s mandate for the report was based on an unjustified assumption of a misalignment between the right to health and intellectual property. As a result of that mandate, the panel called for compulsory licensing, more public funding of R&D and delinking R&D costs from the pricing of medical technologies. (See *BioWorld Today*, Sept. 16, 2016.)

Despite new evidence and a drop in price, the U.K.’s **National Institute for health and Care Excellence (NICE)** is once again refusing to recommend Erbitux (cetuximab) for any head and neck cancer. The agency released draft guidance Tuesday

saying the EGFR inhibitor is not cost-effective. That’s the same conclusion NICE reached in 2009 when it first evaluated the drug and found “uncertainties” in the evidence. Although **Merck KGaA**, which holds the marketing rights to the biologic outside of North America, has addressed some of those concerns, “significant uncertainties remain,” NICE said, adding that it recognized the news would be disappointing for some patients with mouth cancer. Following the agency’s initial denial of coverage, Erbitux was made available for head and neck cancer in the U.K. through the Cancer Drugs Fund (CDF). Until the guidance is finalized, Erbitux will remain available through the CDF, and patients already on the drug will be able to continue their treatment. Comments on the draft guidance are due by Nov. 22. Darmstadt, Germany-based Merck acquired the marketing rights from Imclone Systems Inc., which became part of **Eli Lilly and Co.**, of Indianapolis, in 2008.

Nearly half a year after placing products from **Beijing Taiyang Pharmaceutical Industry Co. Ltd.** on import alert, the **FDA** issued the Chinese company a warning letter this month citing systemic data manipulation and describing what led to the import alert. During an inspection in November 2015, FDA investigators looked through the window of a warehouse that contained drums bearing the company’s label. The investigators were denied entrance to the warehouse until the next day, after “a significant number of drums had been removed,” according to the letter, which was posted to the FDA website Tuesday. Company officials also informed the investigators that the facility had stopped making a certain API two months earlier, but the investigators found electronic audit trails suggesting that recent batches had been made. However, the assay and related substance injection results for the batches had been deleted. The company responded that the test results were from old samples and tests performed for training purposes. The investigators observed that the company relied on falsified and manipulated test results to support batch release and stability data and found that partially completed quality control data worksheets and scratch-paper records containing sample weight values didn’t align with the official quality control data worksheets.

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Pfizer

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combined with “the evolving treatment and market landscape” – translation: slow uptake for the PCSK9 class – Pfizer yanked the late-stage program and terminated the CVOTs.

During the company’s second-quarter earnings call in August, Ian Read, chairman and CEO, suggested continued smooth sailing for bococizumab. He predicted the drug would take its place in the second half of this decade among a handful of commercial assets representing key components “of all of our investment innovation.” That statement followed a report in April that the initial phase III SPIRE-AI study of bococizumab met its co-primary endpoints of percentage change from baseline in LDL-C reduction at 12 weeks compared to placebo and proportion of patients who successfully operated the pre-filled pen. The same month, Pfizer reported the SPIRE-2 CVOT had fully enrolled some 10,500 subjects. An additional CVOT, SPIRE-1, was continuing to recruit, with a goal of enrolling 17,000 subjects, according to Cortellis Clinical Trials Intelligence.

In June, Pfizer said the phase III SPIRE-HR (high risk) and SPIRE-FH (familial hypercholesterolemia) trials met their primary endpoints, showing significant reduction in the percentage LDL-C change from baseline at 12 weeks compared to placebo. Recent top-line results also showed two remaining phase III trials, SPIRE-LDL (low-density lipoproteins) and SPIRE-LL (lipid lowering), met their primary endpoints.

But the more complete dataset suggested bococizumab “is not likely to provide value to patients, physicians or shareholders,” according to the company.

In an email, Evercore ISI analyst Umer Raffat noted that Pfizer’s PCSK9 – a humanized monoclonal antibody (MAb) – differs notably from the approved PCSK9 inhibitors [Repatha](#) (evolocumab, [Amgen](#) Inc.), a human monoclonal immunoglobulin, or IgG2, antibody, and [Praluent](#) (alirocumab, [Regeneron Pharmaceuticals](#) Inc./Sanofi SA), a fully human MAb IgG1 isotype.

“In theory, humanized antibodies still retain certain nonhuman regions (e.g., complementarity determining regions of the variable region, etc.) and thus, in theory, fully human antibodies may carry lower risk,” Raffat pointed out. “This is very product-specific, but it’s [important] to understand,” he added, potentially accounting for differences in hypersensitivity and injection-site reactions seen with bococizumab as well as the suspected relationship between immunogenicity and attenuated efficacy.

The five-year sales forecast for bococizumab was \$716.3 million, according to Cortellis Competitive Intelligence. Pfizer said discontinuation of the program is expected to have a negative effect of approximately 4 cents per share on both a GAAP and adjusted basis, which the company will record as an R&D charge in the fourth quarter.

Pfizer plans to present data from the bococizumab studies at an undisclosed conference, though analysts surmised the company will miss the American Heart Association Scientific Sessions in New Orleans this month, where Amgen plans to present detailed findings on Repatha from the phase III coronary intravascular imaging trial, GLAGOV (GLocal Assessment of Plaque ReGression with a PCSK9 Antibody as Measured by IntraVascular Ultrasound).

Pfizer has two additional hyperlipidemia programs – PF-06427878 and PF-06815345 – in phase I development. Spokesman Steve Danehy told *BioWorld Today* the company “remains committed to working to advance the next generation of medicines that address cardiovascular and metabolic diseases” by targeting key areas of unmet need, including assets to address CVD risk factors such as obesity and its consequences, abnormal glucose metabolism and nonalcoholic fatty liver disease, and to target heart failure directly.

The cardiovascular and metabolic franchise remains “an important therapeutic area of focus for business development,” Danehy added.

‘WE’RE TOO FAR BEHIND’

But the PCSK9 class is facing bigger challenges, and nothing less than a slam dunk will do. During Pfizer’s third-quarter earnings call yesterday morning, Read alluded to the importance of long-term CVD outcomes “as a significant value driver” for lipid-lowering drugs. Tellingly, he added, “We have also recently seen established access restrictions to the class, which has meaningfully dampened our initial expectations for the market potential.”

Indeed, a panel of experts across the drug development supply chain at last week’s Medical Innovation Summit in Cleveland – where Read was a luncheon keynoter – devoted a large chunk of their discussion about drug access and pricing to the PCSK9 class. (See *BioWorld Today*, Oct. 27, 2016, and *BioWorld Insight*, Oct. 31, 2016.)

While Steve Nissen, chairman of cardiovascular medicine in the Cleveland Clinic’s Heart and Vascular Institute, complained that patients with dangerously high cholesterol levels could not get access to PCSK9s, payer and pharmacy benefits manager representatives jumped on the list price of more than \$14,000 per year for the drugs. In comparison, standard of care statins cost about \$250 annually, they said.

Steve Miller, chief medical officer of Express Scripts, and Roy Beveridge, senior vice president and chief medical officer of Humana Inc., predicted anti-PCSK9s will be more widely available for appropriate patients after Amgen reports CVOT data for Repatha, expected in the first quarter of next year.

But the Street has been impatient in recent months about the slow sales trajectories for Repatha and Praluent. (See *BioWorld Today*, May 6, 2016, and Oct. 31, 2016.)

Pfizer has no intention of revisiting the class, according to Read.

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Turnstone

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settings, cancer indications and with different antigenic payloads.

Twelve months ago, Ottawa-based Turnstone raised \$11.3 million in a series A round to take forward a double-mutant Maraba virus strain, MG1, which is attenuated in healthy human cells but highly virulent in cancerous cells. The technology was developed by the company's scientific founders, who are longtime collaborators: John Bell, of the Ottawa Hospital Cancer Center, David Stojdl, of the University of Ottawa, and Brian Lichty, of McMaster University, in Hamilton, Ontario. (See *BioWorld Today*, Oct. 29, 2015.)

The premise originally attached to oncolytic viruses – that they kill cancer cells – was overturned, at least in part, when it became evident during clinical trials over the last decade that their main contribution was immunomodulatory rather than cytotoxic. Local administration of an oncolytic virus helped to elicit an inflammatory milieu within the tumor microenvironment, thereby overcoming the immunosuppressive effects of many cancers. Systemic administration wasn't feasible for the first wave of viruses that reached the clinic, as immune surveillance and complement activation kept their numbers in check.

The first virus to gain approval, Amgen Inc.'s Imlygic (talimogene laherparepvec), a herpes simplex virus strain modified to express granulocyte-macrophage colony-stimulating factor (GM-CSF), has had a minimal commercial impact since its approval 12 months ago. The Thousand Oaks, Calif.-based biotech has yet to report standalone sales for the product, confirming the modest expectations many observers had for its use as a monotherapy. Its real promise lies in combination settings with other agents, such as combination checkpoint inhibitors, where it helps to raise response rates with little or no additional toxicity.

Turnstone is explicitly reviving the oncolytic concept, while also seeking to exploit the immunomodulatory dimension of viral therapy. "We believe it's the most advanced next-generation oncolytic virus and cancer vaccine," Jerel Davis, of Versant Ventures, which led the series A round and also participated in the current round, told *BioWorld Today*. Its MG1 strain acts both as an oncolytic virus and as a cancer vaccine that expresses an antigen of interest that can elicit a strong T-cell response. Moreover, it can be administered systemically because it is a nonhuman virus, with no pre-existing immunity.

A phase I/II investigator-initiated trial in patients with advanced cancers expressing melanoma-associated antigen A3 (MAGE-A3) is ongoing but has already revealed preliminary signs of efficacy.

"The clinical trial results to date have been very encouraging – we're seeing what we'd hoped we would see," Turnstone CEO Sammy Farah told *BioWorld Today*. "Certainly the excitement and strength of that data played an important role in pulling

this financing together."

The deal brings in lead investor Orbimed and another new investor, F-Prime Capital Partners. Turnstone's founding investor, Facit, the commercialization arm of the Ontario Institute for Cancer Research, also participated alongside Versant.

MULTIPLE TRIALS IN THE WORKS

The present study is evaluating a heterologous prime-boost strategy, in which an adenovirus vector expressing MAGE-A3 is administered prior to the Maraba MG1-MAGE-A3 construct. All three arms of the study – the combination plus each of the modified viruses administered as a monotherapy – have completed dose escalation, and dose expansion is now underway. Just 20 patients have been enrolled so far – the final target is 50. A final readout is expected in 2017.

Before the year-end the company is planning to start an open-label phase I/II study of the same construct, in combination with either a programmed cell death 1 (PD-1) inhibitor or a programmed death-ligand 1 (PD-L1) inhibitor in second-line non-small-cell lung carcinoma (NSCLC). It will again follow a prime-boost strategy, employing an adenovirus vector first to induce a T-cell response to MAGE-A3. Interim data should become available during 2017, Farah said.

It will also test the virus in both cervical and head and neck cancers caused by human papillomavirus (HPV). In that setting, it will deploy a version of the MG1 strain engineered to express the E6 and E7 oncoproteins of both HPV16 and HPV18, the two most prevalent strains of the virus.

"We expect that one to kick off by the end of next year," Farah said.

A trial in prostate cancer is in the offing as well. The company also plans to explore MG1's potential in personalized cancer therapy based on neoepitopes specific to individual patients.

The Vero cell expression system it employs for production is sufficiently flexible and has a low cost of goods, Farah said. "Virus manufacturing can be a very complex thing. It's an area where historically the field has run into trouble."

As yet, the company has not announced any deals, be they licensing agreements or research collaborations. Any deal will be driven by clinical or technological considerations rather than cash. "We are exploring partnerships. I don't think the financial drivers are the most important part of that – or even a significant part of that," Farah said. //

FINANCINGS

Aeterna Zentaris Inc., of Charleston, S.C., said it closed its registered direct offering of 2.1 million units at \$3.60 per unit. Gross proceeds totaled about \$7.56 million. Funds will be used to prepare new drug applications for Macrilen (macimorelin) and Zoptrex (zoptarelin doxorubicin). Maxim Group LLC acted as exclusive placement agent, while Rodman & Renshaw and Aegis Capital Corp. served as financial advisors.

Durect

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endogenous, oral small-molecule [DUR-928](#) in patients with nonalcoholic steatohepatitis (NASH), the phase II trial planned for next year will test the drug in acute kidney damage, an indication where today “the only thing they can do is give you fluids and pray.”

Cupertino, Calif.-based Durect unveiled results from the first cohort of the NASH experiment, showing that a single dose of DUR-928, which emerged from the firm’s epigenetic regulator program, provided signals of activity in cirrhotic and noncirrhotic patients. A higher-dose cohort is being enrolled, the company said, and a second phase Ib study is underway in Australia.

The results back a large quantity of preclinical data in 10 animal models altogether. “From a therapeutic safety standpoint, we’ve dosed animals up to 10,000 times the native concentration, and seen no side effects at all, and we’ve safely dosed humans at 1,000 times the native concentration,” Brown said.

“It’s much different from other endogenous molecules. If you think about insulin or erythropoietin or growth hormone or thyroid hormone, any of those, if you were to achieve 10 times the native concentration, you would run into some problems. We’ve had a number of physicians describe [DUR-928] as kind of like the second coming of steroids. It is steroid-based, but it doesn’t work as low down in the receptor level the way steroids do.” So although the side-effect profile is benign, the drug “is in that [steroid] class in its potential efficacy,” he said.

Durect’s open-label, single ascending-dose safety and pharmacokinetic (PK) phase Ib experiment is in liver function-impaired NASH patients and matched control subjects (matched by age, body mass index and gender with normal liver function). It’s being conducted in successive cohorts evaluating single-dose levels of the drug. The first low-dose cohort consisted of 10 subjects with NASH (of which four were cirrhotic and six were not cirrhotic) and six matched control subjects. After a PK/safety review of that cohort, the study has proceeded to the higher-dose group with a dose four times larger. Data from the first cohort showed the PK parameters between the NASH patients and the matched control subjects were comparable.

“We didn’t break down a lot of the details on this because there are still some potential patents here, but a group of biomarkers that we saw – about a half dozen that shifted in the positive direction – were clinical chemistry markers, the kinds of things that [would be tested] if you went to the doctor for your annual checkup,” Brown said, and several more fell outside that category. The study was not designed to assess the efficacy of DUR-928 as a therapy for NASH, but the clinical chemistry biomarkers for liver function and liver injury were reduced 12 hours after dosing. High-sensitivity C-reactive protein, a marker of inflammation, went down, too. Interleukin-18 (IL-18),

an inflammatory mediator implicated in both liver and kidney diseases, decreased in the NASH patients as soon as a few hours after dosing, with the effect more pronounced in cirrhotic subjects at 12 hours. Researchers found little or no change of IL-18 levels in matched control subjects.

What’s more, full-length CK18 (a generalized cell death marker) and cleaved CK18 (a cell apoptosis marker) were reduced after DUR-928 treatment in the NASH patients, with the effect more pronounced in cirrhotic subjects, and with little or no change in the matched controls.

Durect is enrolling and dosing patients in the higher-dose cohort, expected to finish this year, and the single ascending-dose effort should inform future studies. The company has asked for a pre-IND meeting with the FDA in order to launch a future liver disease clinical trial in the U.S.

‘PERSIST’-ENCE PAYING OFF

The second phase Ib study with DUR-928, in Australia, is an open-label, single ascending-dose safety and PK study in patients with impaired kidney function (stages 3 and 4 chronic kidney disease) and matched control subjects with normal kidney function. After a PK/safety review of the low dose, the study may proceed to a higher dose. Assuming both cohorts are dosed, the study will be made up of 16 to 18 subjects, of which 10 to 12 will have received the drug. Results are expected this year.

In that indication, the company had a pre-IND meeting with the cardio-renal group at the FDA at the end of September. Regulators said Durect might win fast track and even, once more data become available, breakthrough status in acute kidney damage.

Laidlaw analyst Jim Molloy said that, with Remoxy’s third complete response letter [CRL] in the rearview mirror, all eyes are geared on Posimir and DUR-928,” and in a research report he called the latest data “promising.” In late September, Austin, Texas-based Pain Therapeutics Inc., a licensee of Durect, said it would ask for a special protocol assessment with regard to new trials demanded by the FDA’s latest CRL for extended-release, abuse-deterrent Remoxy (oxycodone). Still mysterious is why the agency canceled the advisory panel meeting slated for early August, deeming such scrutiny unnecessary – but then sent a CRL. Nor was anyone certain why the FDA didn’t simply grant an extension of the PDUFA date (as done for Pfizer Inc., of New York, with its oxycodone), allowing the company to finish the new trials. (See *BioWorld Today*, Sept. 27, 2016.)

Durect said in April that it had begun making changes wanted by the FDA in the already-started phase III trial called PERSIST with Posimir, an extended-release form of bupivacaine delivered via depot for pain after surgery. The firm was testing Posimir against placebo as a one-time intraneural placement at the close of surgery in patients undergoing laparoscopic cholecystectomy (removal of the gallbladder). Begun in November 2015, the PERSIST trial

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Hypoxia

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brings oxygen to the heart muscle is severely reduced or cut off completely.”

Want to fix the resulting heart muscle damage? Try more hypoxia.

That’s the conclusion of researchers from the University of Texas Southwestern Medical Center, who found that subjecting mice to an atmosphere containing 7 percent oxygen induced proliferation of cardiomyocytes, or heart muscle cells.

The hypoxia induced by the team’s experimental protocol is a far cry from the abrupt lack of oxygen that occurs during an infarct. In their experiments, senior author Hesham Sadek and his team gradually lowered the oxygen concentration in the experimental animals’ air supply over a period of two weeks, and kept them in that low-oxygen atmosphere for another two to three weeks.

Even with time to acclimate, “the animals are not very happy living in seven percent oxygen, which is equivalent to the summit of Everest. . . . This is obviously not a benign environment,” Sadek told *BioWorld Today*.

In fact, to see regeneration, Sadek and his team had to leave the animals under conditions of low oxygen long enough so that the overall mortality rate of animals who had suffered an experimentally induced myocardial infarction was increased by the treatment.

But in those animals that did survive, the proliferation led to improvements in heart function. “Within a few days after they come out, they are normal,” Sadek said.

There were several reasons for Sadek and his team to suspect that hypoxic environments are actually conducive to regeneration.

Sadek, who is an associate professor of internal medicine at UT Southwestern, and his colleagues published their results online in *Nature* on Oct. 31, 2016.

“For years it’s been thought that certain stem cells live in micro-hypoxic niches,” he said, though the effects his team demonstrated are not due to the proliferation of muscle cells, not stem cells. “All our focus has been on myocytes,” he noted.

Another clue is that heart muscle cells stop proliferating at birth, and one of the big differences between prenatal and postnatal life is that “the fetal environment is relatively hypoxic. . . . The heart in particular becomes extremely oxygenated” after birth. And as it does so, it loses the capacity for regeneration.

In the work now published in *Nature*, subjecting the adult mice to hypoxia appeared to cause a general regression of myocytes back to a more prenatal-like state.

Myocytes of the embryo and early postnate are “smaller, proliferative and less oxidative,” Sadek said, whereas at some point soon after birth, they become “larger, oxidative and stop proliferating.”

Spending a few weeks in the good mountain air reprogrammed

myocytes to a lower oxidative state, once again making them smaller and more proliferative while transforming their metabolism to rely more heavily on glycolysis.

Long term, Sadek hopes to test whether inducing hypoxia, or simulating it at the cellular level, can help regeneration clinically. In recent years, work by Sadek and others has shown that it is possible to induce regeneration in heart cells. But those basic research findings have not yet had an impact on clinical practice.

Previous clinical work in altitude physiology, as well as the experience of climbers on Everest, has shown that humans can tolerate hypoxia that is the equivalent of 7 percent oxygen (though at Everest’s summit, the percentage of oxygen in the air is still near 21 percent, the air overall is only a third as dense as it is at sea level).

“We don’t know whether humans with heart damage can tolerate it,” Sadek cautioned. “Animals subjected to 7 percent oxygen are sitting in a hypoxic cage doing nothing.”

One possibility is to combine a less extreme hypoxia – an oxygen content of maybe 10 or 11 percent – with pharmacological mimicry of hypoxia, for example by targeting hypoxia-inducible factor (HIF) or its target genes. Several agents that fit that bill are in clinical trials for different indications. (See *BioWorld Today*, Sept. 13, 2016.)

Sadek said that based on the current state of knowledge, he “wouldn’t rule out environmental hypoxia” as a clinical treatment, but also wouldn’t rule out being able to mimic it pharmacologically.

“If we are able to stimulate the hypoxia pathway in other ways,” he said, “we might not have to put humans under hypoxia.” //

Durect

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was expected to take about a year, enrolling more than 300 patients. U.S. regulators said they want the firm to incorporate standard bupivacaine as an active control in the experiment. During a discussion of earnings Monday, officials said Durect has switched over the majority of active clinical trial sites in PERSIST from part 1 to part 2, in which Posimir is compared head to head against bupivacaine, and continues to add new sites as enrollment goes on. (See *BioWorld Today*, April 11, 2016.) //

APPOINTMENTS AND ADVANCEMENTS

Bioxcel Corp., of Branford, Conn., appointed Peter Mueller chairman of its scientific advisory board.

Caladrius Biosciences Inc., of Basking Ridge, N.J., added Gregory R. Brown to its board, and appointed him to the nominating and governance committee and named him chairman of the audit committee.

Codiak BioSciences Inc., of Woburn, Mass., named Benny Sorensen vice president and head of clinical development.

Gigagen

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Meyer's research examines the role of T-cell populations in immune dysregulation – specifically, the mechanics of how CD1d-restricted invariant natural killer T cells mediate allergy and asthma in mouse models and human clinical samples.

Carter Keller, Gigagen's chief operating officer, was drawn to the company several years ago after previously serving as senior director of marketing at Exelixis Inc., where he led the EU and U.S. commercial launches of cabozantinib (Cometriq) following its approval in the lead indication of medullary thyroid cancer. (See *BioWorld Today*, Nov. 30, 2012.)

Keller, who had earlier marketing, commercialization and strategy roles at Achaogen Inc., of South San Francisco, and Roche Holding AG unit Genentech Inc., shared a connection with Johnson through the Haas School of Business at the University of California, Berkeley, where both received their MBAs.

"I was intrigued by the technology and I was intrigued by what he was doing with it," Keller told *BioWorld Today*, crediting Johnson as "an incredibly smart scientist who was running this company on government grants while building out the technology platform."

In a somewhat fortuitous stroke of timing, cabozantinib's prostate cancer bid "went sideways" about the same time, and Keller, who was planning the prostate cancer launch, saw the opportunity for his own strategic exit.

He didn't look back. In his career moves, "I've been going earlier and earlier, because I like growing companies," Keller said. "Gigagen had an amazing platform and a really strong partnership with big pharma, and I thought we could grow something really well together."

The South San Francisco-based company is seeking to reinvent traditional drug discovery by exploiting a high-throughput single cell sequencing and protein expression platform that uses microfluidics – the core of its patented technology – bioinformatics, next-gen sequencing and genetic engineering to mine B- and T-cell repertoires for full-length, natively paired antibodies and T-cell receptors (TCRs). The platform integrates cell clonal identity, function and target binding across single primary B or T cells in parallel, creating libraries of antibodies or TCRs to express or sequence at the rate of millions per hour – eclipsing conventional methods by several orders of magnitude.

To explain the company's thesis, Keller referenced the rapid remission in former President Jimmy Carter's melanoma following treatment with Keytruda (pembrolizumab, Merck & Co. Inc.) – a response that prompted thousands of patients to clamor for treatment with the PD-1 checkpoint inhibitor.

The obvious problem? "Most people don't respond that way," Keller observed. "So how do we capture Jimmy Carter's immune system and give it to other people? And how do we figure out what, exactly, is working in Jimmy Carter's immune system? Is it a magical antibody? Probably not. Is it a magical T cell?

Probably not. It's probably the interplay among a lot of different factors."

Finding one cell at a time in a test tube – still the most common *modus operandi* for biopharma – is not exactly an efficient way to conduct drug discovery.

"What we've developed, as a platform, allows you to capture the entire immune system and recreate it," Keller said. "And after recreating it, you can give that whole immune system back to a different patient or mine that immune system for the single or multiple elements that are causing the immune response."

The company already has disclosed partnerships with Merck, Novartis AG and COI Pharmaceuticals – the "community of innovation" venture-pharma entity formed by Glaxosmithkline plc and Avalon Ventures – and multiple academic organizations, including Stanford and the University of California, San Francisco. In September, Gigagen inked a collaboration with Cellular Therapeutics Ltd., of Manchester, U.K., to investigate the therapeutic potential of T-cell receptor sequences in tumor infiltrating lymphocytes. Other alliances remain under wraps.

"And we're ready to do our own drug discovery," Keller added.

'FULL HUMAN DIVERSITY ALL THROUGH THE PROCESS'

The company is starting with a recombinant gamma-globulin (rIVIG) therapy designed to treat primary immune deficiencies (PID) – a group of more than 200 disorders characterized by the body's inability to produce antibodies properly, leaving patients susceptible to recurrent and severe infections. Gigagen's rIVIG has higher potency than existing plasma IVIG and lowers the risk for contamination, supply shortage and batch-to-batch inconsistency, Keller explained.

Johnson reported in September during an oral presentation at the European Society for Immunodeficiencies meeting in Barcelona that Gigagen's rIVIG expressed more than 95 percent of the millions of antibodies present in the original input cells, and that expression was stable and consistent in quantity across three weeks of culture. The immunoglobulin G (IgG) monomer was found to be 99 percent pure, and ELISA revealed activity against six pathogens. In mice, an injection of 5 mg of rIVIG showed no obvious signs of toxicity, and the pharmacokinetic profile was similar to plasma IVIG.

The preclinical findings came from applying Gigagen's technology to isolate IgG sequences from millions of antibody-expressing cells, obtained from 50 human donors. The company subsequently generated DNA libraries and used those libraries to express IgG proteins as rIVIG – therapy designed to serve, essentially, as an "antibody transplant" for individuals with PID, Keller explained.

The company is able to capture approximately 3 million B cells per hour, enabling it to corral the antibodies in a given individual's blood – about 50 million in the average human – in a matter of days before recreating them.

[See Gigagen, page 9](#)

Noxopharm

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The company is building out a drug development pipeline focused on drugs that address resistance to chemotherapy and radiotherapy. Lead candidate [NOX66 \(idronoxil\)](#) is the first product to be developed, with later generations of the molecule waiting in the wings.

The company raised A\$715,500 (US\$547,952) in seed funding between 2015 and 2016, and then raised another A\$6 million in its IPO. It's now trading on the Australian Stock Exchange (ASX) under the ticker NOX.

Those funds will allow the company to see NOX66 through proof of concept, CEO Graham Kelly told *BioWorld Today*.

The CEO discovered idronoxil, an isoflavonoid, in the early 1990s when he headed up a research team at the University of Sydney. "We stumbled across this compound, and it didn't take long to realize this was a very active sensitizer of standard chemotherapy," he said. "You could take cancer cells that were resistant to chemotherapy, and you could restore their sensitivity by exposing them to idronoxil."

He said he believes the compound is effective in eliminating resistance mechanisms in cancer cells. Those resistance mechanisms eventually lead all cancers to fail to respond to radiotherapy and chemotherapy, he said.

"Nobody has yet come up with a way to overcome that resistance," Kelly said. "The pharma industry has given up on the notion of drug resistance, and rather than trying to tackle it, the industry is instead looking at other ways to treat cancer such as immunotherapy."

If successful, NOX66 could enable patients to take lower doses of chemotherapy and radiation, making treatment less toxic, allowing patients to continue treatment longer.

Kelly left the university in 1994 and started a company called Novogel, which listed on the ASX and then on Nasdaq in 1998. Novogel ran numerous clinical trials, and while the drug performed "spectacularly in some instances," it wasn't consistent enough to warrant further studies.

Kelly left Novogel in 2006, and the company shut down the program, and the compound was put on the shelf and forgotten. But Kelly couldn't let it go. "Because of my closeness to the drug, it puzzled me for a long time on why it didn't work, and the answer came to me eventually that the problem lay in the way the body treated this drug. The chemical itself is not soluble in water, and the body doesn't like drugs that aren't soluble in water," he said.

Because the body can't eliminate the drug through the urine, it conducts a process called phase II metabolism, which essentially inactivates the drug. "I came up with a way to protect it from phase II metabolism so that the drug does not go through the cycle of being inactivated and reactivated," Kelly explained. "The reformulation of idronoxil is NOX66, and it protects the active ingredient from the deactivation process in the human body."

REFORMULATION REBOOT

Kelly then established private biotechnology company Noxopharm in 2015 to commercialize NOX66.

The new formulation and delivery mechanism is not taken up by the liver, and the technology could be applicable to virtually any water-insoluble drug, Kelly said.

Good candidates for NOX66 will be patients whose tumors have an inherent resistance such as pancreatic cancer, lung cancer or melanoma; however, most cancers develop resistance eventually, so the company is looking at all forms.

Elderly or frail patients or those who elect not to have treatment due to the toxicity of the cancer treatment, could also be good candidates.

The first trial is being conducted in Georgia, and Kelly said the level of regulatory control in the country is comparable to Australia. But because there is less competition for patients, trials can be conducted much more quickly.

The trial will study NOX66 with carboplatin in patients with solid tumors who have failed other forms of therapy. The Georgia study is a few weeks away from enrolling its first patient.

Two other trials are planned that study the drug in combination with radiotherapy.

Unlike many of his Australian peers, Kelly has no plans to out-license his lead compound if it reaches proof of concept. He said he is in it for the long haul, all the way to registration.

Kelly has a different view of the biotech industry. "The market generally thinks it's a good idea to form early partnerships. I disagree. I think you should hang on to your technology and keep your IP.

"There seems to be some vague notion that it's all too hard, but in cancer it doesn't necessarily have to be a long, hard haul," he said. "It's entirely possible to get a drug approved and on the market in less than 200 patients."

Kelly plans on maintaining a lean operation by keeping the company a virtual one. Five people are on staff now, and he may grow it to 10 people, but he doesn't plan on being much bigger than that.

The company is looking at second- and third-generation iterations of NOX66 and is studying epigenetic signaling to better understand what messages the cancer cells send out in response to idronoxil. "The rule in biotech is not to be a one-trick pony," he said.

In the competitive space, he said he doesn't believe any other companies are employing a similar strategy.

The molecule has already been substantially de-risked because it has been tested in more than 400 patients, so "we know an awful lot about it already. We have seen why it didn't work "

No safety issues have been identified with idronoxil, Kelly said, and he's been working with the compound for more than 20 years.

"I know it better than my wife," he quipped. //

Gigagen

[Continued from page 7](#)

Most of the antibodies “don’t do anything,” Keller pointed out. “That’s the dirty little secret. We have to find the very small fraction that fights any particular disease.”

The sequencing technology ensures the company incorporates “full human diversity all the way through the process, to the final product,” Keller added. “We believe we’re the first company to create a millions-diverse antibody polyclonal that can be given to people with primary immune deficiency.”

The company envisions rIVIG as a near-term opportunity that could give it a stake in a product category that represents \$9 billion in annual sales. Beyond rIVIG, Gigagen is seeking to extract antibodies from the immune systems of cancer survivors – those who responded to checkpoint inhibitors. The company uses high-throughput single cell sequencing and expression technology to immortalize the T-cell repertoires and screen them for antitumor function and target binding in vitro.

Wondering what you missed in *BioWorld Insight*?

DRUG DEVELOPMENT CONSTITUENTS REIMAGINE NEW MODEL FOR BIOPHARMA INNOVATION

CLEVELAND – The biopharma industry has found itself between a rock and hard place, or at least that was the premise for a panel of experts across the drug development supply chain that convened at the 2016 Medical Innovation Summit sponsored by Cleveland Clinic Innovations. Breakthroughs in research, biomarkers and genomics offer great potential to develop more effective treatments than ever for a great deal more patients. But is the price more than the market, and patients, can bear? Addressing that question will require collaboration from erstwhile adversaries and, as the discussion made clear, not everyone is on the same page about who makes the next move.

IPF UP AND COMERS LOOK TO ADD ON RATHER THAN COMPETE

With the approval of Esbriet and Ofev two years ago, idiopathic pulmonary fibrosis patients in the U.S. got their first treatment options for the lung disease. But neither drug is a cure, opening opportunities to develop new medications. Rather than compete with the current standard of care though, Fibrogen Inc., Genoa Pharmaceuticals Inc. and others are looking to add on to the currently available offerings.

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This week, the company disclosed the award of a \$1.37 million phase II grant from the National Cancer Institute through the NIH Small Business Innovation Research program, on top of a \$1.5 million NIH grant in September to advance its rIVIG work. Gigagen also is in the process of raising a series A expected to top out at approximately \$20 million, which will enable the company to take the rIVIG program into the clinic in about two years. Once the program has shown proof of concept in humans, the company hopes to secure a big pharma partnership.

Gigagen is confident the rIVIG effort will differentiate its work in the short term and offer a peek at its long-term potential, despite the obvious challenges.

“No one has ever brought a recombinant polyclonal to market,” Keller acknowledged. “We have written confirmation from the FDA that we will be regulated by the blood and blood products group at [the Center for Biologics Evaluation and Research], which is used to seeing diverse mixtures by batch but has never seen a recombinant polyclonal.”

Many of the agency’s questions will be answered during manufacturing scale-up, he said, and the company won’t seek to advance its investigational new drug application until the FDA is satisfied with its enabling batch.

The range applications is immense, according to Keller.

“One of the things we’re doing is capturing blood and bone marrow from vaccinated patients,” he said. “Folks with PID still die of pneumococcus and similar pathogens because they have these troughs of IVIG. We think we can make a better version of IVIG by picking the full millions-diverse library after patients are vaccinated for flu, pneumococcus and other pathogens.”

From there, the company plans to target the immune systems of the Jimmy Carters of the world who responded to cancer treatment and have “an antibody component after the checkpoint is released,” Keller said. “We’ll get it all, and we can give that to other patients. We have a grand vision of what we can do.” //

FINANCINGS

Biohaven Pharmaceutical Holding Co. Ltd., of New Haven, Conn., said it completed an oversubscribed \$80 million private financing. The round was led by Venrock and joined by other biotech investors, including RA Capital Management, Vivo Capital, Aisling Capital, Rock Springs Capital, John W. Childs, Knoll Capital Management, Osage University Partners, Aperture Venture Partners, Connecticut Innovations, Greg Bailey and Litmore Capital. Two undisclosed blue chip pharmaceutical companies also participated in the round as part of in-licensing agreements with Biohaven. Cowen and Co. served as the lead strategic advisor and placement agent for the transaction. William Blair served as a co-placement agent.

Pfizer

[Continued from page 3](#)

"If you asked me would I today begin a new PCSK9 program, the answer is 'no,'" he said on the earnings call. "We're too far behind."

That decision could offer upside for the commercial products, analysts agreed.

"From a commercial standpoint, having one less competitor on the market to pressure pricing is positive for Amgen and Sanofi/Regeneron," wrote Credit Suisse analyst Alethia Young. "A specific concern that we have heard from investors is that Pfizer would likely come in and undercut the price or provide greater rebates to get share in this market. Since we had expected potentially this drug could be on market in 2018, this lowers the threat of pricing risk."

"We view PFE's surprising announcement this morning as a positive headline for both AMGN and REGN," added J.P. Morgan analyst Cory Kasimov. "Nevertheless, while the potential share is now indeed greater for the two on-market PCSK9 assets, a lot is riding on the CVOT data that is expected to provide a launch acceleration for both products."

The stocks were mixed Tuesday, with Amgen shares (NASDAQ:AMGN) off 40 cents to close at \$140.76, while

Regeneron (NASDAQ:REGN) gained \$1.53 to close at \$346.55. Pfizer's shares (NYSE:PFE) fell 64 cents, closing at \$31.07 in heavy volume.

Bococizumab's exit also offered upside for The Medicines Co. (MDCO) and partner Alnylam Pharmaceuticals Inc., which are advancing the RNAi-based PCSK9 ALN-PCS. Elimination of bococizumab as a competitor will enable MDCO to streamline development of its PCSK9 synthesis inhibitor "by opening up the SPIRE-2 population PFE had been pursuing in order to catch up with the two market leaders," Leerink Partners LLC analyst Joseph Schwartz wrote in a flash note.

MDCO previously indicated it was considering how to develop the PCSK9si "in a more efficient manner" by enrolling a high-risk population that could be studied first for LDL reduction and then followed longer for events, Schwartz added. MDCO also can take advantage of its asset's differentiated profile in FH, where MAbs work less well than the PCSK9si, which is agnostic to baseline LDL levels, he added.

"MDCO is now in the cat-bird's seat to be the market disruptor," Schwartz wrote.

Investors seemed to agree, sending the company's shares (NASDAQ:MDCO) to a 3 percent gain of \$1.02, closing at \$33.97. //

FINANCINGS

Tonix Pharmaceuticals Holding Corp., of New York, closed its previously announced underwritten public offering of 9.5 million units, consisting of 9.5 million shares of common stock and warrants to purchase 4.75 million shares of common stock, at an offering price of 55 cents per unit. The underwriter also purchased additional warrants to acquire 712,500 common shares pursuant to the over-allotment option. The warrants have an exercise price of 63 cents per share and are exercisable for a period of five years. Gross proceeds from the offering totaled \$5.2 million. Dawson James Securities Inc. acted as the sole book-running manager. The company expects to use the net proceeds to support the continued development of TNX-102 SL (cyclobenzaprine HCl sublingual tablets) for the treatment of post-traumatic stress disorder (PTSD), including completion of the first interim analysis in the phase III study in military-related PTSD, to further develop other pipeline programs, for working capital and other general corporate purposes.

OTHER NEWS TO NOTE

Allergan plc, of Dublin, completed its \$1.7 billion acquisition of liver disease specialist **Tobira Therapeutics Inc.**, of South San Francisco, a deal first announced in September. About 92 percent of Tobira's outstanding shares were tendered for an up-front cash payment of \$28.35 per share and additional contingent value rights that could yield an additional \$49.84 each, payable upon the successful completion of certain development, regulatory and commercial milestones.

The acquisition added cenicriviroc and evogliptin, two complementary development programs for the treatment of the multifactorial elements of nonalcoholic steatohepatitis, to Allergan's global gastroenterology R&D pipeline. (See *BioWorld Today*, Sept. 21, 2016.)

Amplifi Biosciences Corp., of San Diego, has been granted a small and medium enterprise (SME) designation by the EMA. The designation includes financial support and incentives, including significantly reduced fees for regulatory procedures, including scientific advice, marketing authorizations and inspections, and increased incentives for orphan products. Companies with SME status can also apply for early application to the EMA's priority medicines program, which offers accelerated review times for drugs addressing unmet medical needs. The company is developing bacteriophage therapeutics targeting *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Clostridium difficile*. (See *BioWorld Today*, Aug. 31, 2015.)

Astex Pharmaceuticals Inc., of Cambridge, U.K., said it filed an FDA new drug application for LEE011 (ribociclib) plus letrozole as a first-line treatment for hormone receptor-positive HER2-negative advanced breast cancer, triggering a milestone payment of undisclosed value from Basel, Switzerland-based **Novartis AG**. The application will receive priority review. The drug was developed under a research collaboration between the Novartis Institutes for Biomedical Research and Astex. Under terms of the agreement, Astex is eligible to receive further milestone payments in respect of additional regulatory filings and approvals in Europe and Japan, as well as royalty payments on annual sales of ribociclib should the drug be approved.

OTHER NEWS TO NOTE

Bellicum Pharmaceuticals Inc., of Houston, and Rome-based **Ospedale Pediatrico Bambino Gesù** (OPBG), agreed to expand a collaboration focused on preclinical and clinical development of CD19 and other CAR T and TCR therapeutics engineered with Bellicum's Caspacide molecular safety switch technology. Under terms of the expanded agreement, Bellicum agreed to provide undisclosed financial support to the venture in exchange for exclusive worldwide rights to commercialize certain cell therapies that are developed, while OPBG maintains rights for research purposes. OPBG is expected to start studies in pediatric acute lymphoblastic leukemia and neuroblastoma patients in 2017. In addition, OPBG agreed to manufacture European clinical trial supplies for the investigational programs, as well as Bellicum's PRAME-targeted TCR, BPX-701.

Cempra Inc., of Chapel Hill, N.C., received a \$10 million milestone payment from Toyama Chemical Co. Ltd., a subsidiary of Tokyo-based **Fujifilm Holdings Corp.**, triggered by Toyama progressing to phase III studies with the experimental treatment for community-acquired bacterial pneumonia, solithromycin, in Japan. Toyama owns exclusive rights to develop and commercialize solithromycin in Japan for respiratory tract infections and other indications in adults and pediatric patients. Previously, Cempra had received \$30 million of up-front and milestone payments and can earn an additional \$30 million in payments from Toyama based on the achievement of certain undisclosed objectives. If solithromycin is approved, Toyama would pay tiered royalties, adjusted based on sales, to Cempra following its launch in Japan.

Galena Biopharma Inc., of San Ramon, Calif., said its board approved a reverse stock split of its shares of common stock (NASDAQ:GALE) at a ratio of 1-for-20 on Oct. 26, a move that will allow the company to maintain compliance with the Nasdaq minimum bid price requirement. It will become effective on Nov. 11, and the company's common stock will commence trading on a split-adjusted basis when the market opens on Nov. 14. Company shares plunged in June after an independent data monitoring committee recommended stopping for futility a phase III trial of its experimental cancer vaccine, Neuvax (nelipepimut-S). (See *BioWorld Today*, June 30, 2016.)

Jangobio LLC, a new company launched in Madison, Wisc., will focus on developing cell-based therapies to reverse hormone imbalances associated with aging and mitigate the risk of associated diseases. It is funded by an NIH Small Business Technology Transfer grant and private investments. Craig Atwood, an associate professor of medicine at the University of Wisconsin, Madison, and research director of the school's laboratory for endocrinology, aging and disease, will serve as the company's CEO.

Medivir AB, of Stockholm, entered an agreement with **Karo Pharma AB**, also of Stockholm, regarding the sale of Medivir's

subsidiary, Biophausia AB (Nordic Brands), to Karo. The purchase price will be SEK908 million (US\$101 million) on a cash and debt-free basis, including a normalized working capital. The transaction is expected to close by mid-December. The deal happened as a result of Medivir's board tasking management to investigate a separation of the group's operations into two independent companies, with the aim to separately list the commercial operations. In separate news, Medivir said MIV-818 was selected as a candidate drug from its nucleotide DNA polymerase inhibitor project for the treatment of hepatocellular carcinoma and has now entered nonclinical development.

Neurovive Pharmaceutical AB, of Lund, Sweden, reported preclinical results testing cyclophilin inhibitor NVP-18 in an experimental model of nonalcoholic steatohepatitis (NASH), showing that the drug prevents fibrosis development. In addition, Neurovive said it is developing a new class of compounds with a different mode of action that may offer complementary treatment of NASH.

Oculus Innovative Sciences Inc., of Petaluma, Calif., disclosed the sale of the company's Latin American-related assets to **Invekra S.A.P.I. de C.V.**, of Mexico City, for \$19.5 million in cash. Invekra will provide Oculus a 3 percent payment on all Latin American revenues outside of Mexico, with a minimum payment of \$250,000 per year for the next 10 years, to be paid quarterly in Mexican pesos. Under the terms, \$18 million was already paid as of last Friday, and \$1.5 million was placed in escrow until certain equipment is delivered to Invekra, which is expected in February 2017.

Pharmacyte Biotech Inc., of Laguna Hills, Calif., said it submitted a request for a pre-IND meeting with the FDA for its planned clinical trial in locally advanced, inoperable pancreatic cancer (LAPC). The company has submitted questions to the agency as part of the request. In the trial in patients with LAPC, which is designed to meet a clear unmet medical need for those whose cancer no longer responds after four to six months of treatment with the combination of Abraxane (nab-paclitaxel, Celgene Corp.) plus gemcitabine, one group will receive gemcitabine chemotherapy alone, and the other group will receive the company's pancreatic cancer therapy (encapsulated genetically modified live human cells that can activate the cancer prodrug ifosfamide plus low doses of the prodrug to eliminate side effects from the chemotherapy). In addition to comparing the anticancer activity and safety of the two therapies, a major aspect of the trial will be to determine if, and how well, Pharmacyte's therapy can shrink inoperable tumors so that they become operable.

Pixarbio Corp., of Cambridge, Mass., said it finalized its merger transaction with BMP Holdings, effective Oct. 31, and will submit an application to list on Nasdaq in the fourth quarter. The newly merged company, which is developing a morphine replacement, non-opiate/opioid, non-addictive pain treatment, began trading on the OTC Markets Monday under the ticker PXR.B.

OTHER NEWS TO NOTE

Portola Pharmaceuticals Inc., of South San Francisco, said it expanded its existing clinical collaboration agreement with **Daiichi Sankyo Co. Ltd.**, of Tokyo, to develop Andexxa (andexanet alfa) as an antidote for edoxaban, Daiichi's factor Xa inhibitor. The product is currently under EMA review for reversal of factor Xa inhibition in patients experiencing a life-threatening or uncontrolled bleed and for patients requiring urgent or emergency surgery. As part of the updated agreement, Portola will expand the ongoing ANNEXA-4 study in bleeding patients in Germany. Portola will receive a \$15 million up-front payment and is eligible to receive up to an additional \$10 million upon meeting site initiation and enrollment targets. Upon Andexxa's approval, Daiichi Sankyo will be eligible to receive a low single-digit royalty on product sales up to a total of \$8 million.

Propanc Health Group Corp., of Melbourne, Australia, said it submitted an application for orphan medicinal product designation to the EMA for PRP, a solution for intravenous administration of pancreatic proenzymes trypsinogen and chymotrypsinogen, in the treatment of ovarian cancer. The rationale for developing PRP for intravenous administration in the proposed indication is based on a set of in vitro studies on cancer stem cells generated from ovarian cancer cell lines as well as xenograft and orthotopic mouse models of ovarian cancer. Those data indicate that the dramatic reduction of cellular markers associated with the process of epithelial-mesenchymal transition (EMT) as a consequence of PRP treatment can not only reverse the EMT process with the implication to stop tumor progression and metastasis, but also seem to repress the development of cancer stem cells.

Radiomedix Inc., of Houston, and **Areva Med LLC**, of Plano, Texas, said they were awarded a collaborative Small Business Innovation Research contract grant from the National Cancer Institute to evaluate a targeted alpha-emitter therapy of neuroendocrine tumors, or NETs. A first-in-human study is set to start by the end of next year.

Regenicin Inc., of Little Falls, N.J., said it completed the pre-IND meeting with members of the FDA Office of Cellular, Tissue and Gene Therapies regarding its product, Novaderm, a regenerative cell therapy that has the potential to regrow a patient's own skin in a cell therapy manufacturing facility by harvesting a small, stamp-size skin biopsy. The company is finalizing its IND submission. Novaderm previously gained orphan designation from the FDA.

Signal Genetics Inc., of Carlsbad, Calif., and **Miragen Therapeutics Inc.**, of Boulder, Colo., entered a definitive merger agreement under which the stockholders of Miragen are currently estimated to become holders of approximately 96 percent of Signal's outstanding common stock on a fully diluted basis. The proposed merger remains subject to certain conditions, including approval by Signal's and Miragen's stockholders. In conjunction with the proposed merger, an

investor syndicate comprising existing Miragen investors and new investors has committed to invest about \$40 million in Miragen immediately prior to closing of the proposed merger. The investor syndicate includes Fidelity Management and Research Co., Brace Pharma Capital, Atlas Venture, Boulder Ventures, Jafco Co. Ltd., MP Healthcare Venture Management, MRL Ventures (a venture fund of **Merck & Co. Inc.**, of Kenilworth, N.J.), Reditex Ventures and others. The deal will create a clinical-stage biopharmaceutical company developing micro RNA-targeted clinical candidates for hematological malignancies and pathological fibrosis and preclinical product candidates for cardiovascular and neurodegenerative diseases. The total cash balance of the combined company upon the closing and the financing is expected to exceed \$50 million.

Tapimmune Inc., of Jacksonville, Fla., said a trial on the four class II antigens in HER2/neu breast cancer patients showed that more than 90 percent of patients developed a robust T-cell response against those antigens, amid growing evidence that a mixture of class I and class II antigens is needed for obtaining a robust immune response. As a result, the company said it plans to launch clinical studies next year of its HER2/neu vaccine, TPIV 110, which consists of four class II antigens and one class I antigen, all licensed from the Mayo Clinic.

The Female Health Co. (FHC), of Chicago, said it completed a merger with **Aspen Park Pharmaceuticals Inc.** (APP), of New York, under modified terms, bringing together the former's FC2 female condom product with APP's drug development portfolio. Under the terms, FHC issued 2 million shares of common stock and 546,756 shares of FHC class A preferred stock – series 4 to the APP shareholders.

IN THE CLINIC

Astrazeneca plc, of London, reported results from the phase III SOLO-2 trial testing PARP inhibitor Lynparza (olaparib) as a monotherapy for the maintenance treatment of platinum-sensitive relapsed, BRCA-mutated ovarian cancer, showing a clinically meaningful and statistically significant improvement of progression-free survival (PFS) among patients treated with Lynparza compared to placebo. Median PFS in the Lynparza arm of SOLO-2 substantially exceeded that observed in the phase II maintenance study in patients with platinum-sensitive relapsed ovarian cancer (Study 19). Initial findings demonstrated that the safety profile with Lynparza tablets was consistent with previous studies. Full results of SOLO-2 will be presented at a forthcoming medical meeting.

Axim Biotechnologies Inc., of New York, said it started pharmacokinetic/pharmacodynamics studies with its Canchew Plus Gum, the first cannabidiol hemp oil chewing gum, to determine a reduction of irritable bowel syndrome symptoms in patients. The single-dose study on 10 mg of cannabidiol (CBD) and 30 mg of CBD will determine the concentration of CBD in the blood after chewing one Canchew Plus Gum for 30 minutes, which will determine the administered patient dose for phase II trials.

IN THE CLINIC

Can-Fite Biopharma Ltd., of Petach Tikva, Israel, said it reached agreement with the EMA on the final design of a global, pivotal phase III trial of lead candidate piclidenoson (CF101), an A3 adenosine receptor agonist (A3AR) for psoriasis, and said it intends to start the study in the second half of 2017. The planned randomized, double-blind, placebo- and active-controlled study will investigate the efficacy and safety of daily piclidenoson administered orally as compared to placebo as its primary endpoint and as compared to Otezla (apremilast, Celgene Corp.) as its secondary endpoint in about 400 patients with moderate to severe plaque psoriasis. The primary endpoint will be the proportion of subjects who achieve a Psoriasis Area and Severity Index score response of ≥ 75 percent vs. placebo at week 16. The secondary endpoints will include noninferiority to Otezla on week 32 and efficacy and safety data for CF101 through the extension period of up to 48 weeks of treatment. Patients will be selected to the study based on overexpression of the A3AR biomarker.

Flexion Therapeutics Inc., of Burlington, Mass., reported top-line results from a clinical study testing Zilretta (also known as FX006) on blood glucose levels in adults with osteoarthritis (OA) of the knee who also have type 2 diabetes. Results demonstrated Zilretta is associated with a statistically significant ($p < 0.05$, two-sided) and clinically relevant reduction in the rise of blood glucose compared to that observed following immediate-release triamcinolone acetonide injection in patients who also have knee OA. Zilretta has previously demonstrated clinically meaningful improvement of pain, stiffness and function in its phase III pivotal trial in patients with knee OA. A new drug application is expected by the end of this year.

Ionis Pharmaceuticals Inc., of Carlsbad, Calif., reported phase II data showing that patients with end-stage renal disease on hemodialysis who were treated with IONIS-FXIRx achieved statistically significant, dose-dependent reductions in factor XI (FXI) activity. There were no clinically meaningful reductions in platelet levels and no treatment-related major or clinically relevant nonmajor bleeding events. The placebo-controlled study enrolled 43 patients. In patients treated with 200 mg and 300 mg of IONIS-FXIRx, a mean percent reduction in FXI activity of 56 percent ($p < 0.001$) and 71 percent ($p < 0.001$), respectively,

was achieved at week 13, compared to a mean percent reduction of 4 percent for placebo-treated patients. Furthermore, a decrease in severe clotting events in the dialysis circuit after six weeks compared to baseline was observed. Ionis inked a deal last year with **Bayer AG**, of Leverkusen, Germany, to develop and commercialize the drug for preventing clotting disorders. Upon review of the phase II data and potential advancement of the program by Bayer, Ionis will be eligible to receive a \$55 million payment. (See *BioWorld Today*, May 5, 2015.)

Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, said the *Journal of Clinical Oncology* published detailed results from its phase III TELESTAR study testing telotristat ethyl in patients with carcinoid syndrome. Data from the 135-patient study showed those who added telotristat ethyl to SSA therapy at both the 250-mg and 500-mg doses experienced a statistically significant reduction from baseline compared to placebo in the average number of daily bowel movements over the 12-week study period ($p < 0.001$), meeting the study's primary endpoint. There was also a statistically significant reduction in the levels of urinary 5-hydroxyindole acetic acid, the main metabolite of serotonin, from baseline to week 12 with a reduction of 40 mg/24 hours (250-mg arm) and 58 mg/24 hours (500-mg arm) vs. an increase of 11 mg/24 hours in the placebo arm ($p < 0.001$). Treatment with telotristat ethyl was generally well-tolerated during the double-blind treatment period. Results from a 36-week open-label extension showed sustained bowel movement responses to treatment and no additional safety signals. Additional results showed evidence that telotristat ethyl may also improve stool consistency, reduce the urgency to defecate and reduce the use of rescue short-acting octreotide.

Pluristem Therapeutics Inc., of Haifa, Israel, said the U.K.'s regulator cleared the firm's application for a pivotal phase III trial of PLX-PAD cells in critical limb ischemia for patients unsuitable for revascularization. The program previously was selected by the EMA for its Adaptive Pathways pilot product, which may allow for conditional marketing approval after a single pivotal study. The study will randomize 250 patients to receive 300 million cells or placebo, injected twice intramuscularly two months apart. The primary endpoint will be time to amputation or death, allowing for a survival analysis that is powered to deliver statistically significant results.

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IN THE CLINIC

Renova Therapeutics Inc., of San Diego, said it completed an end-of-phase II meeting with the FDA for its lead gene therapy product, RT-100 AC6 gene transfer, for the treatment of patients with heart failure and reduced ejection fraction. The company said it will proceed with conducting a randomized, placebo-controlled, double-blind phase III trial of a one-time intracoronary administration of adenovirus 5-encoding human AC6 (known as RT-100) for patients with heart failure and reduced left ventricular ejection fraction. The primary endpoint will be the reduction of the event rate of all – first and repeat – heart failure hospitalizations occurring after RT-100 intracoronary injection from baseline to 12 months. Patient safety will continue to be monitored during a follow-up period following completion of the study.

Theravance Biopharma Inc., of Dublin, presented data from several studies of approved antibiotic Vibativ (telavancin), including reports of a retrospective chart review of 32 osteomyelitis patients, showing that 87.5 percent were considered cured or improved at the end of treatment with Vibativ. At three months following treatment, the percentage of patients considered cured or improved increased to 91.3 percent. In that study, *Staphylococcus aureus* was the most common pathogen in 18 of those patients. Results of an in vitro study showed that Vibativ possessed significant activity that was greater than the other antibiotics evaluated against

difficult-to-treat MRSA pathogens from a community hospital in Michigan.

EARNINGS

Incyte Corp., of Wilmington, Del., reported third-quarter net income of \$37 million as compared to a net loss of \$40 million for the same period in 2015. Net revenue from Jakafi (ruxolitinib) was \$224 million vs. \$161 million for the same period in 2015, representing 39 percent growth. R&D expenses grew, hitting \$143 million during the quarter as compared to \$132 million in the third quarter of 2015, driven in part by equity awards to employees and expansion of the company's clinical portfolio. As of Sept. 30, the company had cash, cash equivalents and marketable securities totaling \$717 million. Shares of Incyte (NASDAQ:INCY) rose \$3.06 to close at \$90.03 on Tuesday.

Shire plc, of Dublin, reported a \$387 million net loss for the third quarter and lowered its full-year guidance, citing an increase in integration costs related to its \$32 billion buyout of Baxalta Inc., costs related to licensing SHP647 (formerly Pfizer Inc.'s PF-547659) and reorganization costs associated with the planned closure of a facility in its Los Angeles manufacturing site. The company reported third-quarter revenue of \$3.45 billion, or about \$1.77 billion excluding Baxalta products. Shire shares (NASDAQ:SHPG) closed \$4.12 lower on Tuesday at \$164.52. (See *BioWorld Today*, Aug. 4, 2016.)

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