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Merck to run victory LAP in TGF-beta? Tilos buyout value could reach $773M

By Randy Osborne, Staff Writer

Tilos Therapeutics Inc. CEO Barbara Fox told *BioWorld* that the relationship with Merck & Co. Inc. "went pretty deep pretty fast," culminating in the pharma giant's decision to take over her firm for as much as $773 million. "We never intended to do this," she said. "We always assumed we were going to raise a series A, take these [candidates] forward independently, get some clinical proof of concept and look for partnerships later."

See Tilos, page 3

Genentech's lymphoma treatment Polivy wins accelerated FDA approval

By Michael Fitzhugh, News Editor

The FDA granted Roche Holding AG's Genentech Inc. accelerated approval for Polivy (polatuzumab vedotin), a first-in-class anti-CD79b antibody-drug conjugate, to be taken with bendamustine and Rituxan (rituximab) for adults with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL). The medicine, approved for those who have received at least two prior therapies, got a go-ahead based on complete response rates observed in a randomized, controlled trial. The FDA said it is the first chemoimmunotherapy regimen for the indication.

"Despite meaningful progress in the treatment of diffuse large B-cell lymphoma, treatment options are very limited when the disease is refractory to or recurrent after multiple regimens," said Sandra Horning, Genentech's chief medical officer and head of global product development.

See Polivy, page 4

The faces of pain and addiction, while research sits and access wanes

By Karen Pihl-Carey, Analyst

In a culture that dismisses pain and addiction as laziness or a moral failure, where drug developers find few economic incentives and patients hit treatment access roadblocks, those directly impacted are telling their stories to spur meaningful action.

See Pain, page 5

Gut instinct: Artizan completes series A to hit $12M in funding

By Lee Landenberger, Staff Writer

Artizan Biosciences Inc. has kept a low profile since its creation in 2016, quietly raising money and forging a path to finding a cure for certain diseases involving human intestinal microbiota. It stepped out Monday when it announced completion of a

See Artizan, page 6

The BioWorld Biome

Alpha and Omega

Gut microbe enzymes can convert blood from type A to type O

By Anette Breindl, Senior Science Editor

Scientists have discovered a pair of gut microbial enzymes that worked in tandem to convert blood cells of the type A to those of type O by removing the surface molecule alpha-1,3-linked-N-acetylgalactosamine (GalNAc) from the surface of red blood cells.

If the findings pan out for clinical use, they could help increase the supply of type O red blood cells available for transfusion.

There is an overall shortage of donated blood, which the approach will not fix. But "O blood is coveted blood because it can be universally donated," Stephen Withers told *BioWorld*.

Because of its universal donation capacity, it is also regularly in even shorter supply than other blood types. In the U.S., the Red Cross most

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ADA 2019

Fractyl reverses insulin dependence in T2 diabetes with DMR, GLP-1 combo

By Stacy Lawrence, Staff Writer

SAN FRANCISCO – Type 2 diabetes often becomes progressively more difficult to manage, moving from prediabetes that can be addressed via weight loss and exercise eventually through requiring

See Fractyl, page 8

Newco News

Aussie Pharmaust pins hopes on veterinary drug to treat cancer in humans

By Tamra Sami, Staff Writer

PERTH, Australia – After a AU$2 million (US$1.4 million) capital raise in April, Perth-headquartered Pharmaust Ltd. will advance its lead compound

See Pharmaust, page 9

Other news to note

Avacta Group plc, of Cambridge, U.K., said it selected a specific Affimer molecule (AVA-004) as its clinical candidate, which has been shown to have equivalent tumor growth inhibition to three approved monoclonal antibody inhibitors of PD-L1: Tecentriq (atezolizumab, Roche Holding AG), Imfinzi (durvalumab, Astrazeneca plc) and Bavencio (atezolizumab, Roche Holding AG) in several in vivo animal efficacy models. The molecule will now be moved into clinical manufacturing and IND/CTA-enabling studies, with an IND/CTA application targeted for late 2020 and dosing of first patients shortly afterward. The planned phase I study will be in patients with advanced PD-L1-positive solid tumors. It will explore both intravenous and subcutaneous routes of administration to provide proof of concept with primary endpoints of safety, tolerability and appropriate pharmacokinetics/pharmacodynamics.

Calliditas Therapeutics AB, of Stockholm, and **Everest Medicines II Ltd.**, of New York, said they entered a license agreement to develop and commercialize Calliditas' drug candidate, Nefecon, in greater China and Singapore for the chronic autoimmune kidney disease IgA nephropathy (IgAN). Calliditas will receive an initial up-front payment of $15 million as well as future payments linked to predefined development, regulatory and commercialization milestones up to an additional $106 million, including an option worth up to $20 million for the development of Nefecon in other potential indications. Everest will also pay typical royalties on net sales. The company is currently running a pivotal, global phase III trial with Nefecon for the treatment of patients with IgAN. The agreement gives Everest Medicines exclusive rights to develop and commercialize Nefecon in China, Hong Kong, Macau, Taiwan and Singapore and may, depending on the outcome of consultation with the relevant regulatory authorities, lead to the inclusion of Chinese study centers in the ongoing pivotal study, NefIgArd, with the result of achieving registration approval for the Chinese market on an accelerated basis. Following potential registration approvals, Everest will be responsible for the commercialization of Nefecon in the relevant territories.

Cstone Pharmaceuticals Co. Ltd., of Suzhou, China, said it entered a global clinical collaboration with Bayer Healthcare LLC, part of **Bayer AG**, of Leverkusen, Germany, to evaluate the safety, tolerability, pharmacokinetics and antitumor activity of its PD-L1 monoclonal antibody, CS-1001, in combination with Bayer's regorafenib, an oral multikinase inhibitor (targeting VEGFR, FGFR and CSF1R), as a treatment for multiple cancers, including gastric cancer. This is the first global proof-of-concept study carried out as a collaboration between the two companies. Currently, CS-1001 is being evaluated in seven clinical trials, including five pivotal trials. Regorafenib is approved in more than 90 countries for the treatment of metastatic colorectal cancer and metastatic gastrointestinal stromal tumors and in more than 80 countries for the second-line treatment of advanced hepatocellular.

Deciphera Pharmaceuticals Inc., of Waltham, Mass., said it added a new candidate to its pipeline, DCC-3116, a potential first-in-class small molecule designed to inhibit cancer autophagy, a key tumor survival mechanism, by inhibiting the ULK kinase. Subject to favorable IND-enabling studies and filing and activation of an IND, the company intends to develop DCC-3116 for the potential treatment of mutant RAS cancers in combination with inhibitors of downstream effector targets including RAF, MEK or ERK inhibitors as well as with direct inhibitors of mutant RAS.

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Tilos

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Tentative contacts, though, had begun with would-be partners and "we've been talking to investors up until last week because you never know what's going to happen," Fox said. The synergy between Kenilworth, N.J.-based Merck and Tilos, of Cambridge, Mass., quickly became obvious. "People are looking at the clinical data that are emerging from a number of different sources, from patients on checkpoint inhibitors and other therapies, and finding that transforming growth factor (TGF)-beta is a signal that keeps cropping up as a major driver of resistance," she said.

Merck brings aboard from Tilos a portfolio of antibody prospects that target TGF-beta. Specifically, Tilos deploys candidates that bind to latency-associated peptide (LAP). TGF-beta is secreted as a complex with LAP, which forms a cage around TGF-beta and keeps the cytokine inactive until it's used. Anti-LAP antibodies block the release of TGF-beta from the TGF-beta-LAP complex, which means the technology should knock down TGF-beta activity. The extracellular matrix (ECEM) is believed to store most of the latent TGF-beta in the body, and Tilos' anti-LAP antibodies not only deplete immunosuppressive cells but can inhibit TGF-beta release from inhibitory cells while leaving LAP-TGF-beta in the ECM untouched. Such an approach is meant to inhibit pathological and immunoregulatory processes without disturbing normal tissue homeostasis processes mediated by TGF-beta.

The buyout gives Merck all of Tilos' outstanding shares and includes an up-front payment as well as more if undisclosed milestones are reached, though Fox said she could not provide more detail.

Founders put together Tilos in 2016 based on research by Galina Gabriely and Howard Weiner at the Brigham and Women's Hospital. Weiner's work in autoimmune disease sent him in the direction of LAP and its expression on clinically relevant suppressive cell populations, and the Weiner lab developed antibodies specific for LAP, which showed a strong effect in animal models. Findings published in *Science Immunology* in 2017 found that an anti-LAP monoclonal antibody pushed back tumor growth in mouse models of melanoma, glioblastoma and colorectal carcinoma. Anti-LAP effects included decreasing LAP-positive CD4 T cells and blocking the release of TGF-beta. Other efforts published two years earlier in *Nature Communications* identified and characterized LAP-expressing gamma-delta cells.

Tilos, which takes its name from an island in the Aegean Sea and contains an acronym for tumor-infiltrating lymphocytes, was established by Boehringer Ingelheim Venture Fund and Partners Innovation Fund, with added funding provided by Shangpharma Innovation Fund. About $10 million has been brought into Tilos, which employs fewer than 10 people and will become a wholly owned subsidiary of Merck. Fox will step down from her full-time role and serve as a consultant, she said, though others – including Chief Scientific Officer Jessie English – will stay on.

Scholar Rock, GARP bids comparable

Drug developers are exploring many ways to hit TGF-beta, from antibodies at Basel, Switzerland-based Novartis AG and Sanofi SA, of Paris, to small molecules at Indianapolis-based Eli Lilly and Co. and Pfizer Inc., of New York. "The overall approach that we've taken is supported by other things in the field as is always the case, but we have a unique handle on the biology of what's been happening, based on decades of work in our founder's lab," Fox said. She called the Tilos effort "similar although distinguishable" from Scholar Rock Holding Corp., of Cambridge, Mass., which last December struck a deal in fibrosis with Foster City, Calif.-based Gilead Sciences Inc. The pact included $80 million up front – $50 million in cash and $30 million in Scholar Rock common shares – along with a one-time milestone payment of $25 million when certain preclinical studies are completed. More could come later, with $1.425 billion in potential payments across three programs in the form of research, development, regulatory and commercialization milestones. Scholar Rock also is eligible for high single-digit to low double-digit tiered royalties on product sales. Gilead took exclusive options to license global rights to candidates emerging from three TGF-beta programs, including inhibitors said to target activation of latent TGF-beta1 with high specificity, inhibitors that selectively target activation of latent TGF-beta1 localized to the ECM and a third, undisclosed, TGF-beta1 discovery program. (See *BioWorld*, Dec. 20, 2018.)

Another firm with projects underway in the realm is North Chicago-based Abbvie Inc., which has a deal with Argenx SE, of Breda, the Netherlands. Abbvie is taking forward a first-in-class Argenx antibody, ARGX-115 – more recently dubbed ABBV-151 – to target TGF-beta1 signaling indirectly by inhibiting glycoprotein A repetitions predominant (GARP), a cell-surface protein involved in TGF-beta1 activation. Also, Merck KGaA, of Darmstadt, Germany, and London-based Glaxosmithkline plc, in February signed an agreement worth up to €3.7 billion (then US$4.2 billion), including €300 million up front, to co-develop Merck's fusion protein, M-7824 (bintrafusp alfa). The compound, which entered the clinic in 2015, is designed both to sequester TGF-beta within the tumor microenvironment and to block the immunosuppressive activity of PD-L1. It's made up of the extracellular domain of human TGF-beta receptor II linked to an antibody fragment derived from Merck's marketed anti-PD-L1 antibody, Bavencio (avelumab). (See *BioWorld*, Feb. 6, 2019, and March 15, 2019.)

Fox said Scholar Rock's research is "really the closest" to Tilos', though different nomenclature is used to describe the program and the level of selectivity in various environments may differ. As for Abbvie's GARP push, one could "certainly look at them as comparable," she said. "We think we're better." ♦

Polivy

Continued from page 1

DLBCL is the most common form of non-Hodgkin lymphoma and is generally responsive to first-line treatment. But as many as 40% of patients will relapse, at which time salvage therapy options are limited and survival is short, Genentech said. In the U.S., about 25,000 new cases of DLBCL are expected to be diagnosed this year.

Polivy is expected to be available to patients immediately and will priced at about $90,000, which covers a fixed course of about four months, with dosing every three weeks for six cycles. Cost will vary to some degree, though, because dosing is weight-based. The Rituxan element of therapy will cost about $39,500 over the course of the four-month regimen, while bendamustine's cost will vary depending on its source.

The green light is Genentech's sixth FDA approval in the last six months, and its fifth blood cancer medicine to gain approval, the company said.

Polivy employs an anti-CD79b antibody conjugated to the tubulin polymerization inhibitor monomethyl auristatin E developed using Seattle Genetics Inc.' antibody-drug conjugate technology, an approach thought to minimize the effects on normal cells. The drug is also being investigated for the treatment of several types of non-Hodgkin lymphoma.

The FDA's approval in r/r DLBCL was based on the results from the phase Ib/II GO29365 study, which Genentech said was the first and only randomized pivotal trial to show higher response rates over bendamustine plus Rituxan (BR), a commonly used regimen in people with r/r DLBCL who are ineligible for a hematopoietic stem cell transplant. Results of the study showed that 40% of people treated with Polivy plus BR achieved a complete response (95% CI: 25-57), meaning no cancer could be detected at the time of assessment, compared to 18% with BR alone (95% CI: 7-33). Complete response rates were assessed by independent review committee.

The study also showed that 45% of people on Polivy plus BR achieved an objective response at the end of treatment (95% CI: 29-62), compared to 18% of people treated with BR alone (95% CI: 7-33). Among trial participants treated with Polivy plus BR who achieved a complete or partial response, 64% had a duration of response (DOR) lasting at least six months vs. 30% of people treated with BR alone. Additionally, 48% of people treated with Polivy plus BR had a DOR lasting at least a year as compared to 20% of people treated with BR alone.

Adverse reactions occurring in at least 20% of patients, and at least 5% more frequently in patients treated with Polivy plus BR compared to BR alone, included low white blood cell count, low platelet levels, low red blood cell count, numbness, tingling or pain in the hands and feet, diarrhea, fever, decreased appetite and pneumonia.

Continued approval of Polivy for the indication is, as is typically the case with drugs securing accelerated approval, contingent upon verification and description of clinical benefit in a confirmatory trial.

In addition to its priority review, Polivy was recognized as a breakthrough therapy by the FDA and has landed a PRIME designation from the EMA.

Other medicines approved for the treatment of r/r DLBCL include the CAR T-cell therapies Yescarta (axicabtagene ciloleucel, Gilead Sciences Inc.) and Kymriah (tisagenlecleucel, Novartis AG). (See *BioWorld*, Oct. 20, 2017.) ♦

Other news to note

Evotec SE, of Hamburg, Germany, said it entered a five-year partnership with the Bill & Melinda Gates Foundation to discover new treatment regimens targeting tuberculosis. Evotec will receive a grant of about $23.8 million. The main objective is to generate standardized, high-quality preclinical data to support novel regimen selection and development.

Flex Pharma Inc., of Boston, said that Institutional Shareholder Services Inc. and Glass Lewis are recommending that shareholders vote in favor of all agenda items at the company's June 14 special shareholders meeting, including its proposed transaction with **Salarius Pharmaceuticals LLC**, a Houston-based clinical-stage oncology company. In January, Flex Pharma and Salarius signed a definitive merger agreement under which privately held Salarius will merge with a wholly owned subsidiary of Flex Pharma. Flex stockholders will own about 19.9% of the combined company and Salarius investors will own the remainder.

In the wake of a $225 million settlement to resolve separate criminal and civil investigations into its marketing of the sublingual fentanyl spray Subsys, Phoenix-based **Insys Therapeutics Inc.** is filing for bankruptcy under Chapter 11 of the U.S. Bankruptcy Code. The company said its goal is to facilitate the sale of its assets and to address its legacy legal liabilities. Meanwhile, management plans to use cash on hand and operating cash flows to support continued operations, they said. Company shares (NASDAQ:INSY) fell 51.5% to close at 64 cents on Monday.

Pain

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Nicole Hemmenway, interim CEO, U.S. Pain Foundation

"It has been heartbreaking for me to read the messages that we get from legitimate patients that say that they are being forced to taper off medications with no other viable solutions," said Nicole Hemmenway, interim CEO of the U.S. Pain Foundation. "I cannot tell you the amount of messages that I receive from people saying that because of lack of options they are considering suicide."

Hemmenway spoke last week at the Biotechnology Innovation Organization's international convention in Philadelphia during an afternoon of panels tackling issues faced by people with pain and addiction. The sessions included input from patient advocates, providers, an FDA official, biopharma executives and even a surprise visit from Pennsylvania Gov. Tom Wolf, who declared a medical emergency in his state in January 2018 following sky-high statistics in heroin overdoses.

Danielle Friend, director of science and regulatory policy, BIO

Danielle Friend, director of science and regulatory policy at BIO, said although health care costs for pain are astronomical, investment in the space is low, only about 3.6% of total drug development venture funding, possibly due to low clinical trial success rates. BIO data indicate that only 2% of novel pain drugs advance from phase I to approval, compared with 10% of drugs for all other diseases.

The pain pipeline consists of 220 drug programs in the clinic, with 125 testing novel chemical entities, 87% of which are non-opioid receptors, Friend said.

For addiction, there are 15 active programs in the clinic for novel compounds, but BIO identified only $16 million invested across two addiction-focused companies over the last 10 years.

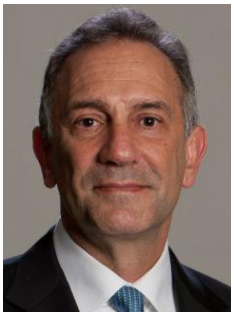
Gary Mendell, the founder, chairman and CEO of the nonprofit advocacy group Shatterproof, knows all too well the ripple effects of addiction and the lack of investment in research. His son, Brian, spent eight years at eight different treatment centers fighting the disease. On Oct. 20, 2011, in the middle of the night, Mendell's cell phone rang. Brian had committed suicide.

"I picked it up and was told that my son had just died. He was 25 years old. He hadn't used a substance in 13 months," Mendell said. "Even more tragic, it wasn't just addiction that took my son's life. It was the feeling of shame that he had every morning when he opened his eyes, feeling like an outcast."

The U.S. CDC reports that 10% of all suicides are committed by people in pain.

It is a subject rarely talked about, said Kathleen Broglio, a nurse practitioner and an assistant professor at the Geisel School of Medicine at Dartmouth College in Hanover, N.H. She works directly with seriously ill patients, many with cancer, who also have substance abuse disorders. She often prescribes Suboxone (buprenorphine and naloxone) so patients can be treated for their pain without relapsing into addiction.

> *"All of this information was sitting in peer-reviewed medical journals, and hardly any of it was in use.*
>
> Gary Mendell
> CEO, Shatterproof



The biggest problem in New Hampshire, she said, is access, with 50% of all rural areas without a single buprenorphine provider. Although the Comprehensive Addiction and Recovery Act of 2016 now allows nurse practitioners and physician assistants to provide medications for addiction treatment, they must receive 24 hours of training to do so, compared with eight hours required for physicians.

"We've put so many barriers on the provider," Broglio said. "I've got to complete the 24-hour training. Then I have to keep special records. I have to be ready for the DEA to come in at any point now. But I don't have to do any of that to prescribe as many opioids as I want to treat my patient's cancer pain."

Massachusetts is the only state, Mendell said, that requires coursework for pain management and addiction prevention treatment at its medical and nursing schools. He said he believes other states should follow suit, but that the X waiver, which enables health care workers to prescribe addiction treatments, should be removed from under the Drug Enforcement Administration umbrella.

Another roadblock to access is insurance coverage. Broglio has wanted to increase the dose of Suboxone for certain patients, but cannot get it covered: "I'm saying, 'OK, but you're paying $28,000 a month for their cancer-related treatment and you're telling me that you don't want to give me 8 milligrams more a day to help deal with their addiction?'"

Lack of new treatments

BIO's report, Volume II: Pain and Addiction Therapeutics, said costs for treating pain in the U.S. is estimated at $635 billion annually and costs for substance abuse is $700 billion a year. Chronic pain affects about 100 million people in the U.S., and addiction affects more than 23 million Americans. Over the past decade, the FDA has approved only two new chemical entities to treat pain, as well as 12 abuse-deterrent formulations.

Currently approved pain drugs work via 12 main mechanisms, including cyclooxygenase inhibitors (acetaminophen, ibuprofen, naproxen), opioid receptor modulators (morphine, codeine, heroin, oxycodone, fentanyl), direct sodium channel blockers (lidocaine, benzocaine, bupivacaine), and serotonin receptor agonists (sumatriptan, frovatriptan, zolmitriptan).

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Artizan

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series A funding round totaling $12 million.

The funding allows the company to be in the clinic in about two years, to relocate its lab from Yale University in New Haven, Conn., to the city's Science Park, and to more than slightly double its staff size. The company has nine scientists on its payroll. Artizan's platform, IgA-SEQ, is used to identify the putative disease-driving bacteria in inflammatory bowel disease from the intestinal microbiota in humans with the goal of developing new and potentially curative treatments.

James Rosen, CEO, Artizan

"We've achieved our early corporate goals. We've demonstrated there are disease-driving bacteria in the human gut and that we can identify those targets," Artizan's president and CEO, James Rosen, told *BioWorld*. "We have the data in preclinical models but we have not published any of it. It's still proprietary."

The data suggest, Rosen continued, that specific bacteria in the human gut cause disease and if certain strains from humans are put into Artizan's preclinical model, it can then produce spontaneous disease in animals. Those diseases include not only inflammatory bowel disease but also ulcerative colitis and Crohn's disease. It also targets microbiota-driven diseases such as obesity, metabolic syndrome, autoimmune disease and a variety of skin, lung, liver and central nervous system diseases.

"These bugs we've identified are bugs that are taken from human beings with that target disease. We have a cohort of 300 identified patients who have provided samples to us that we've analyzed and compared to healthy cohabitants, people who live with the person with the disease," Rosen said. "We also have 100 people in a sample database who are healthy and not related to anyone we've identified. We compare the microbiota of the healthy and compare it with those infected. Then we take the human bug and put it in the animal model to spontaneously produce that disease. When the animal gets sick, we can apply the therapy either to neutralize or eliminate the disease. Our target is a cure."

Paul Miller, a 30-year biopharma veteran, was also appointed chief scientific officer (CSO). Most recently Miller was CSO of Synlogic Inc. Previously, he was vice president of infection biology at Astrazeneca plc and led discovery teams at Pfizer Inc. that produced eight drug development candidates and provided research support for several successfully marketed antibiotics, including Zithromax (azithromycin) and Zyvox (linezolid). A trained microbial geneticist, Miller received his PhD in microbiology and immunology from the Albany Medical College and conducted post-doctoral studies at the NIH. He has also served as a member of the Institute of Medicine's Forum on Microbial Threats.

Artizan is a product of a research agreement with Yale University, where its founders, Richard Flavell, Noah Pal and Marcel R. de Zoete, worked to address diseases involving intestinal microbiota. The company has an exclusive license from Yale to apply the platform to drug development, Rosen said.

Investors in Artizan include Hatteras Venture Partners, Malin Investments, Johnson & Johnson Innovation – JJDC Inc., Osage University Partners and Elm Street Ventures. Artizan also entered a collaboration agreement with Brii Biosciences to commercialize in China up to three programs in the Artizan portfolio upon achievement of clinical proof of concept.

Rosen is after that proof of concept for a series B fundraising that is planned for later this year. As it stands, even with this series A money, it's not enough to sufficiently get the company into the clinic.

"It'll be plus or minus $30 million, allowing us to go through preclinical development," Rosen said.

Artizan isn't the only company in the gut game. Seres Therapeutics Inc.'s top-line results from its SER-287 phase Ib placebo-controlled induction study in 58 patients with mild to moderate ulcerative colitis showed the microbiome therapy containing a consortium of live bacterial spores resulted in a benefit in clinical remission rates. There was also an improvement in mucosal appearance by endoscopy. The SER-287 safety and tolerability profile, a co-primary study endpoint, demonstrated no clinically significant safety findings.

Second Genome Inc. is also studying the link between gut microbiome and irritable bowel disease as well as other metabolic disorders such as obesity and type 2 diabetes and nonalcoholic steatohepatitis. ♦

Other news to note

Mateon Therapeutics Inc., formerly of South San Francisco, has moved to Agoura Hills, Calif., following the completion of its merger with **Oncotelic Inc.** In connection with the relocation, Amit Shah will be appointed as chief financial officer, effective July 1. (See *BioWorld*, April 26, 2019.)

Oncternal Therapeutics Inc., of San Diego, said its reverse merger with **Gtx Inc.**, of Memphis, Tenn., closed on June 7. The combined company will retain the Oncternal name and trading symbol, ONCT. Immediately following the completion of the merger, the former stockholders of Oncternal held approximately 77.5% of the outstanding shares of common stock of the combined company. The law firm Kahn Swick & Foti LLC is pursuing a securities class action lawsuit against Gtx in the U.S. District Court for the Southern District of New York, alleging that "the S-4 registration statement filed in connection with the merger provides materially incomplete and misleading information about Gtx's financials and the transaction." (See *BioWorld*, March 8, 2019.)

Pfizer Inc., of New York, is the object of an investigation by the law firm Kahn Swick & Foti LLC. The investigation is focused "on whether Pfizer's officers and/or directors breached their fiduciary duties to Pfizer's shareholders or otherwise violated state or federal laws," the law firm said. The inquiry is associated with what the firm identified as "a wide-ranging lawsuit brought by 44 state attorneys general alleging an illegal conspiracy to inflate prices" on generic drugs.

Blood

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recently sounded the alarm in mid-May that it was down to a two-day supply of type O blood for emergency rooms.

Blood types are determined by the presence or absence of two separate sugars, on the surface of red blood cells. Individuals with GalNAc on their red blood cells have type A blood, while those with galactose (Gal) are type B, and those with both types of sugars are type AB. (Blood can also be Rh-positive or Rh-negative, which is determined by a surface protein. The enzymes discovered by Withers and his colleagues do not affect Rh type.)

GalNAc and Gal are far from the only sugars on cells. "Every cell in our body is coated in very specific sugars," Withers said, and those sugars are "a little bit like the baggage label on a cell – they identify something about the cell, and how it interacts with its environment."

Withers is a professor of chemistry and biochemistry at the University of British Columbia, and the senior author of the findings, which were reported in the June 10, 2019, issue of *Nature Medicine*.

Such sugars are also antigens, and while people are immune tolerant to the antigens of their own blood type, they will have a violent, potentially fatal reaction to red blood cells with the wrong antigen. In that sense, GalNAc and Gal are more like labels advertising their carrier's fealty to FC Barcelona or Real Madrid, respectively. If you have one label, showing up in the opposing team's stronghold is a bad idea.

Type O red blood cells have neither GalNAc nor Gal on their surface, and so can be used to transfuse everyone, regardless of blood type. (The situation is the opposite with plasma, the fraction of the blood that contains no cells but serves as a conduit for nutrients and antibodies. Because individuals with blood type AB make antibodies to neither GalNAc nor Gal, they are universal plasma donors.)

In a perfect world, there would be no increased need for type O blood. Both donors and recipients would roughly mirror the general population, which consists of about 45% type 0, 40% A and 10% B, with the remainder of the population being type AB.

However, in dire emergencies, there may not be time to identify an individuals' blood type – or that individuals' blood type may be in especially short supply at that moment.

Mining the microbiome

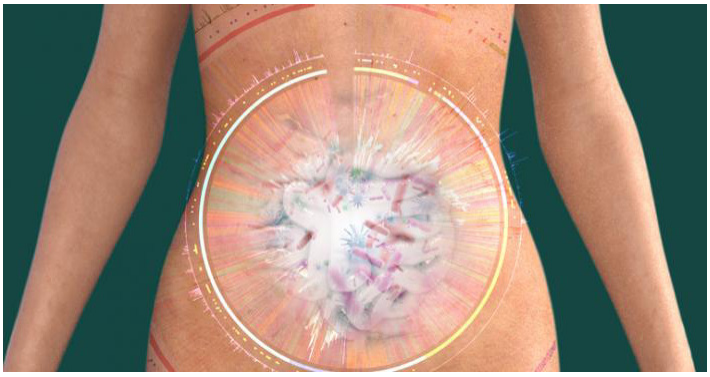
In principle, the idea of removing the antigens from red blood cells to convert them into type O blood is "not a new concept," Withers noted.

But enzymes capable of doing so that had been previously identified were either not efficient enough or not specific enough to make them viable candidates for large-scale use.

Withers and his team found such enzymes by mining the gut microbiome.

Withers described his lab's original discussions about where to look for a bacterium that degrades blood.

"Grave-robbing," he said with deadpan humor, "wasn't seriously considered," which left very few species such as mosquitoes and leeches that feed on human blood.



Above: The gut microbiome can be mined for useful enzymes. Credit: Spencer Phillips/EMBL-EBI

Left: A unit of red blood cells for transfusion. Credit: Canadian Blood Services

However, "in parallel, we were quite well aware that mucins" – heavily glycosylated proteins that are the principal component of the mucus that lines the gut, as well as the airways and the female reproductive organs – are composed of a number of sugars," including the same sugars that determine blood type.

Gut bacteria, he said, are "opportunistic little devils," and it seemed likely that someone in the more than 1,000 known species of gut bacteria had figured out how to clip the sugars from mucins, and use them as a food source.

Metagenomic screening confirmed that hunch. The commensal species *Flavonifractor plautii* produced two enzymes, FpCBM32 and FpGH36, that worked together to turn red blood cells from A to O in a two-step procedure.

The team will continue to look for better enzymes, Withers said, but "the principle focus is on… extremely important but much less exciting part of massive safety testing."

For now, he said, "we don't know for sure that our enzyme isn't chopping something else off of a red blood cell as well." His team is working with Canadian Blood services "to make sure converted blood is completely safe."

Even if the approach is found to be safe enough for broad use, Withers does not envision type A blood routinely being converted; there would be an albeit small additional cost to doing so, and it's "probably always easier to give the right type of blood."

But recombinantly produced enzymes could be used to alleviate acute shortages of type O blood.

"The big advantage here would be in inventory control," he said. "That's where blood services see the need." ♦

Fractyl

Continued from page 1

multiple daily insulin injections. A novel procedure could offer the opportunity to turn back the clock for type 2 (T2) diabetes patients who are insulin-dependent.

Fractyl Laboratories Inc. has developed an outpatient procedure known as duodenal mucosal resurfacing (DMR) that, when used in combination with a GLP-1 receptor agonist drug, can reverse the need for insulin for type 2 diabetes patients who were previously insulin-dependent. That's according to data from a small study presented Sunday at the American Diabetes Association's 79th Scientific Sessions (ADA).

T2/NAFLD indication

The Lexington, Mass.-based startup is also working to demonstrate efficacy in patients with fatty livers, known as nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH), with the latter being a more severe subset of the former. It reported data supportive of that indication recently, alongside further data in this study.

Fractyl plans to aim for a treatment label specifically in type 2 diabetes patients with NAFLD/NASH, indications that are both related to metabolic dysfunction and commonly co-exist in the same patient. At least 40% – and possibly as high as 80% – of T2 diabetes patients have NAFLD as a co-morbidity, according to the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

"Our type 2 diabetes trials are designed to investigate not just the effects of the treatment on blood sugar, but also its effects on other aspects of metabolic syndrome, most notably the effect that it has on liver fat. Patients with type 2 diabetes are at particularly high risk of downstream liver and other metabolic complications," Harith Rajagopalan, co-founder and CEO of Fractyl, told *BioWorld*.

Fractyl expects to have data soon from two randomized, sham-controlled trials: Revita 2 in type 2 patients on oral agents and the investigator-backed study Domino in women with insulin resistance and polycystic ovarian syndrome (PCOS). Revita 2 is slated to report this summer, while Domino data will be out in the fall. The startup also is currently enrolling a U.S. pilot study; after that completes, Fractyl plans to file with the FDA for a pivotal U.S. study around year-end.

The Revita DMR system already received a CE mark in 2016. It works by resurfacing the inside of the duodenum, which is the upper part of the small intestine. The procedure is thought to work because the duodenum thickens, changing texture and altering the microbiome, with the high fat and high sugar diet that is characteristic of populations in the most economically developed countries.

It was originally developed after anecdotal observations that bariatric surgery patients were experiencing significant blood glucose reduction, often preceding or irrespective of subsequent weight loss. The outpatient DMR procedure could offer a viable option for type 2 diabetes patients who are unwilling to submit to bariatric surgery; and the procedure itself has the potential to be repeatable, if its effects diminish over time and/or with the resumption of poor dietary habits.

> *"Other than extreme interventions, this is the first same-day treatment that has the potential to free patients with advanced type 2 diabetes from daily insulin injections.*
>
> Jacques Bergman
> Amsterdam UMC

INSPIRE data

"Other than extreme interventions, this is the first same-day treatment that has the potential to free patients with advanced type 2 diabetes from daily insulin injections," said Jacques Bergman, a professor of gastroenterology at Amsterdam UMC and principal investigator of the INSPIRE study. "Our results suggest we can use a straightforward and safe outpatient procedure to eliminate the need for daily insulin, which could have a meaningful positive impact on the hundreds of millions of people across the world suffering from type 2 diabetes."

The results just presented at ADA were for the 16-patient INSPIRE study, which focused on T2 diabetes patients who have used long-acting insulin for more than two years. The pilot study found that six months after Fractyl's DMR procedure, 13 of the 16 patients were insulin-free. Management with a once-daily or one-weekly GLP-1 subcutaneous injection was sufficient to manage blood glucose levels.

Novo Nordisk A/S, of Bagsværd, Denmark, also recently submitted to the FDA for the first oral version of GLP-1 agonist semaglutide. That could offer the prospect of transitioning many type 2 diabetes patients who currently require intensive glucose monitoring and management with multiple daily insulin injections instead to an outpatient procedure followed by a single daily GLP-1 oral medication.

The INSPIRE pilot study also found an average reduction of liver fat of almost 45%, from a baseline of 8.5% liver fat as measured by an MRI-PDF, alongside improvements in blood pressure and weight reduction.

Mechanism of action

Fractyl is preparing to submit a publication on its preclinical research to better elucidate the mechanism of action at work in DMR, which is slated to come out later this year. The system has already been used in more than 200 patients; it was well-tolerated and has shown sustained improvements in blood glucose levels, insulin resistance measures, liver fat, cardiovascular risk markers and weight loss, unaided by any lifestyle changes through one year of follow-up.

"We've been doing a lot of work to try to understand on a detailed molecular, cellular level what is actually changing in the duodenum in response to high-fat and high-sugar diets. That may be contributing to the cause of metabolic syndrome and insulin resistance," said Rajagopalan.

He continued, "We've been working with leading scientific

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Pharmaust

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monepantel into phase I trials in humans.

An Australian researcher discovered that monepantel – an already approved antiparasitic drug for food chain animals sold by Novartis Animal Health – was potent as a cancer drug, Pharmaust CEO Roger Aston told *BioWorld*. "I looked at it and thought it was a good opportunity for repurposing an already-approved drug that's in the veterinary market and sold in Europe, Australia and New Zealand. The drug is sold for sheep and food chain animals, so it had to be very safe."

Roger Aston, CEO, Pharmaust

Aston, however, did have some questions. "This initially raised some alarm bells for me. How could you have an anticancer drug going into the food chain?" He took the product on board and conducted extensive preclinical work, looking at 40-odd human cancer cell lines that showed the drug was active at both stopping tumor growth and killing tumors.

Richard Mollard, chief scientific officer, Pharmaust

Monepantel is an oral aminoacetonitrile (AAD) that modulates the mTOR pathway, which plays a role in the pathogenesis of diseases like Alzheimer's disease, Parkinson's disease and other aging disorders. In addition, mTOR inhibitors have been approved for indications including renal cell carcinoma, breast cancer, mantel cell lymphoma and pancreatic neuroendocrine tumors.

The market for mTOR inhibitors is valued at more than AU$2 billion per year.

Aston was previously the CEO of Pitney Pharmaceuticals, which began development of monepantel. Pharmaust acquired Pitney in 2013 for roughly AU$5 million. Pharmaust already had a subsidiary called Epichem that was involved with medicinal chemistry, and the company now has two distinct business units, with Epichem acting as a contract medicinal chemistry company and Pharmaust as a drug development company.

For the last year, Pharmaust has focused on reformulating the drug so it would be practical to give orally as a treatment in both veterinary cancers and human cancers.

Phase I trials positive

The company completed a small phase I trial in solid tumors that achieved primary endpoints in safety and reduction in clinical biomarkers.

Pharmacodynamic analysis showed treatment was associated with a significant reduction in two key biomarkers associated with the disease. Clinical assessment using RECIST 1.1 showed that of the four patients who completed the trial, three had stable disease and one patient had progressive disease.

"In both humans and dogs, monepantel is metabolized to monepantel sulfone, and this metabolite remains in the body for some time," said Pharmaust Chief Scientific Officer Richard Mollard.

"This metabolite appears to have the same, targeted cytotoxic effect upon cancer cells and the same nontoxic effect upon noncancer cells as monepantel. This means that monepantel and its metabolite are predicted to provide an enduring and specific effect through a 'double kick' to cancer cells, while minimally affecting normal cells in the body.

"We have the safety and toxicology data, and we already know we have a very safe drug as we go into the phase I trial," Mollard added, noting that the drug has already demonstrated anticancer activity in humans as far as pharmacodynamic markers and showing stable disease.

"We've been able to give quite high doses, and there hasn't been much evidence of toxicity, and the product exhibited tumor regression or progression-free survival in phase I trials," Aston said.

Because the drug doesn't harm the immune system, it allows a patient's immune system to build up while the tumor is also held in check to give the body time to fight it.

"Our strategy is about protecting the immune system and keeping the tumor in check. The hope is that patients will be able to be treated for years," he said. "The concept is different than normal cancer therapy, which wipes out the immune system. I don't think [this approach] has been considered."

The plan is to focus on cancers that have a poor prognosis such as esophageal, pancreatic and gliomas, since those patients have limited options.

Man's best friend could live longer

Since the drug is already approved for animals, it is also being tested in canines as a cancer therapy treatment for pets. And the path to market for veterinary indications should be quite fast.

"Roughly 80% of dogs that have cancer end up being put down," Aston said, "and we estimate that the animal cancer market in itself is worth about AU$500 million to AU$600 million, and there is a lot of room for a drug that doesn't have toxicity."

The company is beginning a phase II trial in canines, which is part of an agreement with Elantel, a subsidiary of Eli Lilly and Co. If the trial is successful, the product will likely be acquired by Elantel, which has an option on it.

"We're working with a company that owns our product, but we own the methods of use," he said.

"Often what happens in dogs, happens in humans, so the outcome of the dog trial will be an important pointer for us on what's going to happen in humans. If we can show stable disease for long periods of time, we believe we can target several cancers in humans."

In late March, Pharmaust reported that its phase I canine trial showed no adverse effect, toxicity or safety-related observations. Another study showed that one tablet was sufficient to provide blood levels associated with anticancer activity.

See Pharmaust, page 10

Pain

Continued from page 5

FDA-approved treatments for opioid use disorder include opioid receptor antagonists (naltrexone, naloxone), opioid receptor modulators (buprenorphine) and an opioid receptor agonist and nicotinic acetylcholine receptor antagonist (methadone).

The lack of new treatments in the addiction space is a sobering fact that drives Mendell. While his son worked to overcome his disease, a young neighbor faced a cancer diagnosis, and the community rallied around him, cooking meals, organizing bake sale fundraisers, and helping the family find the best treatments available. In contrast, Mendell and his wife could not find any addiction treatments that were based on science.

He said he often thinks about Brian's last visit home before his suicide.

"He looked at me and he said, 'Dad, I wish that someday people would understand. I'm not a bad person'," Mendell said. "'I'm a good person with a difficult disease. I'm trying my absolute hardest.'"

Following Brian's death, Mendell uncovered studies, some funded through "tens-of-billions-of dollars" in grants from the NIH, showing through randomly controlled trials the ability to significantly reduce the numbers of people dying from addiction, and the ability to improve outcomes and treatment.

"Yet all of this information was sitting in peer-reviewed medical journals, and hardly any of it was in use," he said.

Through Shatterproof, Mendell has brought together 21 insurers representing 250 million people who have formed a consensus on eight principles of care. The organization also is working toward a quality measurement system, greater facility resources, and most importantly, the elimination of stigma.

Likewise, Hemmenway described pain patients who face stigmas that they are lazy or overdramatic. Unrelenting, invisible, chronic pain, she said, is felt by numerous Americans, and she herself has lived with pain since 1994, with no use of her right hand and minimal use of her arm for many years.

"When the disease was at its worst, I was confined to a bed or to a wheelchair. What worked best for me, at that time, was taking high doses of pain medications," she said. "Over the course of several excruciating years, I was fortunate to find a combination of non-pharmaceutical treatments that really worked to manage my pain, but I also know that I am one of those lucky ones. I was lucky to have the support of a family and the financial help to access these treatments. So many people do not."

Editor's note: See the next issue for a look into how government and industry responds to issues facing patients with pain and addiction. ♦

Fractyl

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experts and it dovetails very nicely with a growing body of evidence from investigators all around the world that high fat and sugar diets actually cause changes to the intestinal lining and the microbiome, and that there are changes that are occurring in the duodenum that seem to be intimately associated with insulin resistance. And we believe that our therapy is beginning to show evidence that we are reversing these processes."

Fractyl hasn't done a financing since a $44 million series D round in November 2017. The company has an impressive and deep-pocketed syndicate; that round was led by an undisclosed new investor and joined by new investors GV, True Ventures, and IDO Investments. Existing investors included General Catalyst, Bessemer Venture Partners, Domain Associates, Mithril Capital Management, Emergent Medical Partners and Deerfield Management.

Rajagopalan declined to comment on Fractyl's current fundraising status, but an additional cash infusion seems likely to precede a costly U.S. pivotal trial. With a few crossover investors already in its syndicate, the startup may be weighing when to test the IPO waters. ♦

Pharmaust

Continued from page 9

Earlier this month, the company announced a capital raise of AU$2 million via a pro-rata non-renounceable rights offer of 80 million new shares priced at AU2.5 cents each.

The funds will allow Pharmaust to begin the larger phase I human trial and the phase II canine trials.

"If you look at the company's share price, we're a microcap, and yet here we are going into a major phase II trial. This is very typical of the Aussie market; they want to see you reach your goal before we get funding," Aston said.

Pharmaust shares on Australia's Security Exchange (ASX:PAA) were trading at AU3.7 cents. Its market cap is roughly AU$10.4 million. ♦

Other news to note

Roche Holding AG, of Basel, Switzerland, and Philadelphia, Pa.-based **Spark Therapeutics Inc.** said they each received a second request for additional information and documentary material from the U.S. Federal Trade Commission in connection with the FTC's review of Roche's pending acquisition of Spark. In addition, the U.K. Competition and Markets Authority has opened an investigation in order to obtain further information in relation to Roche's proposed acquisition of the company. Roche said its offer, which was previously scheduled to expire on June 14, has been extended until July 31.

Sorrento Therapeutics Inc., of San Diego, said review of early results from an ongoing "declawed cat pain trial" run by its Ark Animal Health division has prompted management to explore use of resiniferatoxin as a local nerve block injection for the control of neuropathic post-amputation residual limb pain in humans. A full IND package is being prepared for FDA submission in the second half of 2019. Resiniferatoxin binds to TRPV1 receptors and selectively ablates the nerve endings responsible for pain signals experienced by patients, Sorrento said.

Sosei Group Corp., of Tokyo, and its partner, **Pfizer Inc.**, of New York, have nominated for development a new clinical candidate from their multitarget drug discovery collaboration. Sosei Heptares will receive a $3 million milestone payment from Pfizer for the achievement. The first clinical candidate under the collaboration was nominated by Pfizer in May 2019. The collaboration was signed in November 2015 to research and develop potential new medicines directed at up to 10 GPCR targets across multiple therapeutic areas and came with a $33 million equity investment by Pfizer into Sosei Heptares. (See *BioWorld*, Dec. 1, 2015.)

Financings

Biondvax Pharmaceuticals Ltd., of Jerusalem, said it is conducting a rights offering to holders of the company's American depositary shares (ADSs) who will receive 0.537823255 ADS rights for each ADS owned. Proceeds from the offering will be used to fund operations, including completion of an ongoing pivotal phase III trial of M-001 universal flu vaccine candidate, and scale up of the M-001 production process. The company anticipates results of the trial by the end of 2020.

Oncologie Inc., of Boston, said it closed an $80 million series B financing, which will be used to advance its three clinical-stage programs, as well as its biomarker platform and in-licensing activities. The company plans to initiate key clinical trials in the coming months, including a global proof-of-concept gastric cancer study with its lead compound, bavituximab, in combination with Keytruda (pembrolizumab, Merck & Co. Inc.). Bavituximab is an investigational immune-modulatory monoclonal antibody that targets phosphatidylserine, a phospholipid that inhibits the ability of immune cells to recognize and fight tumors. Its other programs include a TLR9 activator, lefitolimod, and a VEGF-targeting antibody, varisacumab.

Regulatory front

Saying it wanted to allow adequate time for response, the **FDA** reopened the comment period on its draft guidance "Quality considerations for continuous manufacturing" that was released in February. The guidance is intended to provide greater predictability and quality around the adoption of continuous manufacturing for drug products, helping to resolve potential issues some companies have as they consider switching from a batch to continuous manufacturing process, especially when it comes to how that switch might impact FDA review timelines. The new comment deadline is Aug. 10.

The U.S. **Federal Trade Commission** (FTC) last week updated procedures for filing agreements under the Medicare Prescription Drug, Modernization and Improvements Act (MMA). As of June 17, those agreements must be filed electronically by emailing them to both the FTC at mma@ftc.gov and the Antitrust Division of the Department of Justice at mma@usdoj.gov. Companies will receive an emailed confirmation letter, along with a tracking number for use in future correspondence about the filing, the FTC said. The filing requirements apply to certain agreements between generic and brand companies, biosimilar and reference biologic sponsors, generics companies, and biosimilar companies. Recent amendments to the MMA expanded the types of documents that must be submitted with an agreement, including other agreements the parties enter into within 30 days before or after the relevant agreement.

Clinical data for June 10, 2019

Company	Product	Description	Indication	Status
Phase I				
Adverum Biotechnologies Inc., of Menlo Park, Calif.	ADVM-022	Gene therapy using AAV.7m8 carrying an aflibercept coding sequence under control of expression cassette	Wet age-related macular degeneration	First patient dosed in second cohort
Aerpio Pharmaceuticals Inc., of Cincinnati	AKB-9778	Binds to and inhibits vascular endothelial protein tyrosine phosphatase	Primary open-angle glaucoma	First patient dosed
Homology Medicines Inc., of Bedford, Mass.	HMI-102	Gene therapy delivering functional copy of phenylalanine hydroxylase gene to liver cells	Phenylketonuria	Trial begun
Phase II				
Dr. Reddy's Laboratories Ltd., of Hyderabad, India	PPC-06	Methylhydrogen-fumarate prodrug	Moderate to severe plaque psoriasis	Met both co-primary endpoints of PASI-75 and IGA scores of 0 or 1 with at least a 2-point reduction from baseline after 24 weeks of oral treatment
Intelgenx Corp., of St. Laurent, Quebec	Montelukast Versafilm	Leukotriene receptor antagonist	Alzheimer's disease	Added trial site; first patient completed 26 weeks
Sienna Biopharma-ceuticals Inc., of Westlake Village, Calif.	SNA-120 (pegcantratinib)	Tropomyosin receptor kinase A inhibitor	Psoriasis	Showed statistically significant improvement compared to vehicle on pre-specified endpoints of psoriasis disease severity, including Investigator's Global Assessment 2-grade composite, comprising a 2-grade improvement from baseline and clear (0) or almost clear (1) skin
Phase III				
Aptinyx Inc., of Evanston, Ill.	MYX-2925	NMDA receptor modulator	Fibromyalgia	Top-line results from 23-patient study showed statistically significant effects on primary endpoint, brain activity biomarkers associated with central pain processing, measured using advanced imaging techniques; statistically significant and clinically meaningful improvements also observed on secondary patient-reported endpoints, including pain scores, the Revised Fibromyalgia Impact Questionnaire and other fibromyalgia symptom scales; brain activity biomarkers and improvements in patient-reported pain were correlated; company planning larger, 12-week study in second half of 2019 to test patient-reported outcomes as primary endpoint
Innovate Biopharma-ceuticals Inc., of Raleigh, N.C.	Larazotide acetate	Renormalizes dysfunctional intestinal barrier	Celiac disease	Started trial
Tetraphase Pharmaceuticals Inc., of Watertown, Mass.	Xerava (eravacycline)	Fully synthetic fluorocycline	Complicated intra-abdominal infections	3 studies further evaluating approved compound showed clinical cure rates of 89% and 88.6% for Xerava and comparators, respectively; in patients with non-appendiceal cIAIs clinical cure rates were 88.8% and 89.7%, respectively

Notes

For more information about individual companies and/or products, see Cortellis.

Regulatory actions for June 10, 2019

Company	Product	Description	Indication	Status
Acucela Inc., of Seattle	Emixustat hydrochloride	Inhibits RPE65	Stargardt disease	EMA granted orphan designation
Altimmune Inc., of Gaithersburg, Md.	Heptcell	Immunotherapeutic comprising 9 synthetic peptides from HBV proteome with T-cell epitope identification method	Hepatitis B virus	Completed pre-IND meeting with FDA regarding phase II design; agency did not object to study design or to plans for manufacturing and product testing; agency also did not recommend any additional studies in preparation for IND submission
Eloxx Pharmaceuticals Inc., of Waltham, Mass.	ELX-02	Eukaryotic ribosomal selective glycoside	Cystinosis	Received authorization of its CTA from Health Canada for a phase II trial
Evolus Inc., of Newport Beach, Calif.	Nuceiva (prabotulinumtoxinA-xvfs)	900 kDa purified botulinum toxin type A	Moderate to severe glabellar lines	European Commission requested supplementary information as part of the MAA review, which could delay standard timeline; EMA's Committee for Medicinal Products for Human Use issued positive opinion April 26, 2019
Novavax Inc., of Gaithersburg, Md.	Resvax	RSV fusion protein recombinant nanoparticle vaccine	Respiratory syncytial virus	FDA recommended an additional phase III trial to confirm efficacy against medically significant RSV disease in infants born to mothers vaccinated with Resvax
Sesen Bio Inc., of Cambridge, Mass.	Vicinium	Locally administered fusion protein	High-risk, Bacillus Calmette-Guerin unresponsive non-muscle invasive bladder cancer	Completed type B pre-BLA meeting and reached alignment with FDA on accelerated approval pathway, along with rolling review; company expects to initiate BLA submission in fourth quarter of 2019

Notes

For more information about individual companies and/or products, see Cortellis.

Conference data: American Diabetes Association (San Francisco)

Company	Product	Description	Indication	Status
Astrazeneca, of Cambridge, U.K.	Farxiga (dapagliflozin)	SGLT2 inhibitor	Type 2 diabetes	In a subanalysis of the 17,160-patient phase IIIb Declare-TIMI study, Farxiga produced a 47% reduction within the relative risk of kidney function decline, end-stage renal disease (ESRD), or renal death (excluding cardiovascular death) compared to placebo ($p<0.0001$); risk of end-stage renal disease or renal death was 0.1% for Farxiga compared to 0.3% for placebo ($p=0.012$); ESRD incidence was 0.1% for Farxiga compared to 0.3% for placebo; acute kidney injury occurred in 1.5% and 2% of patients treated with Farxiga and placebo, respectively
Boehringer Ingelheim GmbH, of Ingelheim, Germany, and Eli Lilly and Co., of Indianapolis	Jardiance (empagliflozin)	SGLT2 inhibitor	Type 2 diabetes	Post-hoc analysis of Empa-Reg Outcome trial indicated consistent effect on reducing cardiovascular and renal risks in adults with type 2 diabetes and known cardiovascular disease, who also have a form of chronic kidney disease without overt proteinuria
Cohbar Inc., of Menlo Park, Calif.	Analogues related to CB-5064	Mitochondrially encoded peptide	Type 2 diabetes	Preclinical data showed improvements in body weight and glucose tolerance in diet-induced obese mice and showed selective agonism at the apelin receptor, a key cell surface receptor involved in regulation of glucose utilization, fluid homeostasis and cardiovascular function
Dance Biopharm Holdings Inc., of Durham, N.C.	Dance 501	Inhaled, preservative-free human insulin	Type 2 diabetes	Results from phase II Samba 04 trial showed faster onset of action vs. comparable doses of subcutaneously administered insulin lispro; greater action in first hour of administration vs. lispro at all 3 doses with median relative differences of 107%, 57% and 45% ($p<0.05$)

Company	Product	Description	Indication	Status
Diasome Pharmaceuticals Inc., of Cleveland	HDV-L	Hepatocyte-directed vesicle technology	Type 1 diabetes	Met primary endpoint in phase IIb Isle-1 study of noninferiority when mixed with Lispro vs. Lispro in HbA1C at 26 weeks
Eli Lilly and Co., of Indianapolis	Tirzepatide	GIP and GLP-1 receptor agonist	Type 2 diabetes	In a subanalysis of a phase 2b study, the improvements in insulin sensitivity markers observed in tirzepatide-treated patients were only partially attributed to weight loss; in a phase II study, dose escalations with tirzepatide produced A1C reductions up to 2% and weight loss up to 5.7 kg and fewer gastrointestinal side effects; in an 8-week trial in Japanese patients, tirzepatide reduced A1C up to 2.05% and body weight up to 5.1 kg; in a phase IIb study, treatment with tirzepatide improved NASH-related markers; company plans to start a phase IIb study in NASH later this year
Eli Lilly and Co., of Indianapolis	Ultra rapid lispro (URLi)	Mealtime insulin	Type 1 and type 2 diabetes	In the phase III Pronto-T1D and Pronto-T2D studies, URLi was noninferior to Humalog for A1C reduction from baseline to 26 weeks; URLi was superior to Humalog for reduction in blood glucose spikes at both 1 hour (-27.9 mg/dL [T1D], -11.8 mg/dL [T2D]) and 2 hours (-31.2 mg/dL [T1D] and -17.4 mg/dL [T2D]) after a test meal
Eli Lilly and Co., of Indianapolis	Trulicity (dulaglutide)	GLP-1 receptor agonist	Type 2 diabetes	In the 9,901-patient phase III Rewind study, Trulicity reduced the risk of major adverse cardiovascular events (MACE 3) compared to placebo (HR=0.88); the reduction was consistent across subgroups: established cardiovascular disease (HR=0.87), no established cardiovascular disease (HR=0.87), baseline A1C greater than or equal to 7.2% (HR=0.86), baseline A1C less than 7.2% (HR=0.90), women (HR=0.85) and men (HR=0.90); all 3 components of MACE 3 contributed to the risk reduction compared to placebo: CV death (HR=0.91), nonfatal heart attack (HR=0.96) and nonfatal stroke (HR=0.76); Trulicity reduced composite microvascular outcomes (HR=0.87); Trulicity produced a 0.46% reduction in A1C compared to 0.16% reduction for placebo; weight loss was 2.95 kg for Trulicity and 1.49 kg for placebo
Mannkind Corp., of Westlake Village, Calif.	Afrezza (insulin)	Inhaled insulin	Type 1 and type 2 diabetes	In a pediatric study, drug produced early postprandial glucose control within the first hour post-dose; company plans to run a phase III pediatric study; in type 2 diabetes patients on 2 or more therapies, adding Afrezza resulted in a mean decrease in A1C of about 1.6%; 13 of 14 patients achieved A1C below 8% from a mean baseline of 9.1%; hyperglycemia was reduced by 74%; time in range increased by 75%; in type 1 diabetes patients, Afrezza provided significantly better glucose control in the first 2 hours following the meal; Afrezza treatment was associated with lower rates of overall and level 2 hypoglycemia
Novo Nordisk A/S, of Bagsvaerd, Denmark	Oral semaglutide	GLP-1 receptor agonist	Type 2 diabetes	In the phase IIIa Pioneer 2 study, oral semaglutide produced an A1C reduction of 1.3% compared to a 0.9% reduction with Jardiance (empagliflozin, Ingelheim GmbH) at 26 weeks ($p<0.0001$); A1C reduction at 52 weeks was also statistically significant; weight reduction was 3.8 kg for oral semaglutide at both 26 and 52 weeks and 3.7 kg and 3.6 kg for empagliflozin, respectively; in the phase IIIa Pioneer 4 study, oral semaglutide was noninferior to Victoza (liraglutide) for reduction in A1C (1.2% vs. 1.1%, respectively) and superior to placebo (1.2% vs. 0.2%, respectively); at week 52, oral semaglutide produced statistically significant reductions in A1C vs. both Victoza (1.2% vs. 0.9%, respectively) and placebo (1.2% vs. 0.2%, respectively); weight reduction was 4.4 kg for oral semaglutide, 3.1 kg for Victoza and 0.5 kg for placebo) at 26 weeks and 4.3 kg for oral semaglutide, 3 kg for Victoza and 1 kg for placebo at 52 weeks
Provention Bio Inc., of Oldwick, N.J.	PRV-031 (teplizumab)	Anti-CD3 monoclonal antibody	Type 1 diabetes	In the At Risk study of 76 patients who had 2 or more type 1 diabetes (T1D) autoantibodies and abnormal glucose metabolism, patients treated with a 14-day course of PRV-031 had a median time to clinical diagnosis of T1D of 48 months, compared to just over 24 months for patients receiving placebo ($p=0.006$); 72% of the placebo group developed clinical diabetes compared to 43% of the PRV-031 group

Company	Product	Description	Indication	Status
RISE Consortium	Metformin, insulin glargine or liraglutide	Antihyper-glycemic, insulin and GLP-1 receptor agonist	Impaired glucose tolerance (IGT) or newly diagnosed type 2 diabetes	In the Restoring Insulin Secretion (RISE) study of adults, treatment with metformin for 12 months or 3 months of insulin glargine followed by 9 months of metformin or liraglutide with metformin reduced A1C compared to placebo, but there were no sustained improvements in beta-cell function in any treatment group at 3 months after treatment withdrawal; in the RISE pediatric study, beta-cell function deteriorated both during treatment and after treatment withdrawal, with no differences between the 2 treatment groups: 3 months of insulin glargine followed by 9 months of metformin or 12 months of metformin alone
Sanofi SA, of Paris	Soliqua (insulin glargine and lixisenatide)	Insulin and GLP-1 receptor agonist	Type 2 diabetes	In the 514-patient phase III Lixilan-G study, patients switching to Soliqua had a 1.02% reduction in A1C levels compared to a 0.38% reduction for patients who continued on their GLP-1 receptor agonist (RA) (p<0.0001); 62% of patients taking Soliqua achieved an A1C below 7% compared to 26% of patients continuing on GLP-1 RA; 43% of patients taking Soliqua had an A1C below 7% with no documented symptomatic hypoglycemia of 70 mg/dL or less compared to 25% of patients continuing on GLP-1 RA
Sanofi SA, of Paris	Toujeo (insulin glargine)	Insulin	Type 2 diabetes and moderately to severely impaired renal function	In the Bright study, 462 patients taking Toujeo had a 1.72% reduction in A1C compared to a 1.3% reduction for 462 patients taking Tresiba (insulin degludec, Novo Nordisk A/S); there were no differences in the rates of hypoglycemia
Sihuan Pharmaceutical Holdings Group Ltd., of Hong Kong	Janagliflozin	SGLT2 inhibitor	Type 2 diabetes	In a study of healthy Chinese subjects, drug was well-tolerated and 25-mg and 50-mg doses were determined to be further investigated; phase III studies underway
Veroscience LLC, of Tiverton, R.I.	Circadian Neuroendocrine Resetting Therapy	Readjusts aberrant clock controlled biochemical physiology	Nonalcoholic steatohepatitis, obesity, prediabetes and type 2 diabetes	Preclinical data showed treatment inhibited NASH progression and reversal of existing fibrotic NASH in murine model systems; in models of obesity, prediabetes and type 2 diabetes, the treatment produced lasting benefits on glycemic control long after the cessation of therapy
Zafgen Inc., of Boston	ZGN-1061	MetAP2 inhibitor	Type 2 diabetes	In a phase II study, ZGN-1061 improved postprandial glucose excursion in a mixed-meal tolerance test at week 12 (p<0.001 for both the 0.9-mgand 1.8-mg doses); there were trends for improvement in insulin levels; using a modeling approach, beta-cell function (p=0.02) and insulin sensitivity (p=0.07) improved in an exploratory combined analysis of the two doses

Notes

For more information about individual companies and/or products, see Cortellis.