



Biotrinity 2019

AI, big data to tackle metabolic disease via genetics, behavior

By Nuala Moran, Staff Writer

LONDON- Artificial intelligence and big data are poised to address the complexity of metabolic diseases, drawing out specific genetic and environmental factors that can inform discovery and development of new therapies and providing the means to modify behaviors which underlie those conditions.

“These tools are starting to come into play and we are optimistic it will start to yield therapies,” said

See Biotrinity, page 3

G1 eyes 2020 NDA, MAA for trilaciclib

By Lee Landenberger,
Staff Writer

G1 Therapeutics Inc. plans to submit marketing applications in the U.S. and Europe next year based on FDA feedback from the company’s end-of-phase II meeting for trilaciclib, a myelopreservation agent designed to protect bone marrow from damage from chemotherapy.

The NDA and MAA submissions will be based on data from three randomized, double-blind, placebo-controlled small-cell lung cancer (SCLC) trials. G1 reported positive results from all three in 2018. G1’s NDA follow-up meeting is later this year with the EMA MAA meeting soon after. Neither is on the calendar as yet.

“We’re working out details of how the FDA wants to see the analyses,” Jeff Macdonald, G1’s spokesman told *BioWorld*. “There’s a certain level of complexity. We have three trials looking at different patient populations. You might have a single endpoint with one study and another with a number of endpoints.”

The timing is dependent upon

See G1, page 4

Vividion hatches series B: \$82M funds ‘golden eggs’ trio bound for POC work

By Randy Osborne, Staff Writer

Vividion Therapeutics Inc. CEO Diego Miralles told *BioWorld* that \$82 million in new series B money will propel research to “clinical proof of concept in at least one of the three lead programs, if not more” as the company – just over a year after sealing a pact worth \$101 million up front that brought Celgene Corp. aboard as a collaborator –

See Vividion, page 5

Lawmakers look upstream to stem increasing Medicare drug spend

By Mari Serebrov, Regulatory Editor

Even as legislation advances in the U.S. Congress to make prescription drugs more affordable for Medicare beneficiaries, lawmakers continue to search for a solution to the problem itself.

“We’ve talked about a number of strategies

See Medicare, page 7

Kerastem completes phase II study of hair regrowth cell therapy, plans phase III

By Annette Boyle, Staff Writer

Kerastem Technologies LLC reported that the U.S. FDA accepted its 12-month phase II study and the company plans to begin a phase III study of its cell therapy-based hair regrowth system in early 2020 with an as-yet-identified distribution partner.

See Kerastem, page 9

The BioWorld Biome

Inflammation triggers accumulation

MS joins diseases featuring protein aggregates

By Anette Breindl, Senior Science Editor

Researchers have discovered that the synaptic protein Bassoon accumulated in the neurons of mice with experimental autoimmune encephalitis, the closest animal model to multiple sclerosis (MS), causing neuronal damage in much

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Newco News

Startup Polyprox taking biologic approach to targeting protein degradation pathways

By Cormac Sheridan, Staff Writer

DUBLIN – Polyprox Therapeutics Ltd. is the latest contender to enter the promising but increasingly crowded space of harnessing the proteasome for therapeutic effect. The company, a newly launched spinout from the University of Cambridge, is based on more than a decade of research conducted by its founder and chief scientific officer, Laura Itzhaki, who is professor of structural pharmacology at Cambridge and an expert on protein structure, protein folding, protein-protein interactions and protein engineering.

Cambridge, U.K.-based Polyprox has raised £3.4 million (US\$4.4 million) in seed funding as a prelude to a much larger series A round, which

See Polyprox, page 8

Financings

Bexion Pharmaceuticals Inc., of Covington, Ky., said its board and shareholders approved the increase of series B preferred stock financing to \$25 million. Of that, \$16.6 million has been collected to date. Proceeds will support an ongoing adult phase I trial testing safety of BXQ-350, plus the initiation of two additional clinical trials. A phase I trial in pediatric patients with brain tumors and rare solid tumors opened earlier this month. A phase II adult glioblastoma multiforme trial is set to start later this year. After the completion of the latest round, Bexion said it will have raised more than \$48 million in private investment and more than \$6 million in nondilutive funding from the National Cancer Institute.

Bicycle Therapeutics Ltd., of Cambridge, U.K., has filed an S-1 for an IPO, aiming to raise up to \$86 million through the sale of American depositary shares (ADSs), though the number of ADSs and price have not yet been disclosed. Bicycle, which develops drugs called Bicycles, described as fully synthetic short peptides, seeks to list on Nasdaq under the ticker BCYC. Bookrunners include Goldman Sachs & Co. LLC, Jefferies, Piper Jaffray and Canaccord Genuity.

Codiak Biosciences Inc., of Cambridge, Mass., filed for an IPO, aiming to raise \$86 million, though the number of shares and share price have not yet been disclosed. The company seeks a Nasdaq listing under the ticker CDAK. Jefferies, Evercore ISI and William Blair are the joint bookrunners on the deal. Codiak, founded in 2015 to develop exosome-based therapeutics, inked a potential \$1 billion deal with **Jazz Pharmaceuticals plc**, of Dublin, early this year. (See *BioWorld*, Jan. 4, 2019.)

Helix Biopharma Corp., of Richmond Hill, Ontario, said it closed a second tranche of a private placement financing for gross proceeds of CA\$510,000 (US\$379,996). The company is working on completing another private placement tranche by May 17.

Helix intends to use the net proceeds for working capital and research and development activities.

Ideaya Biosciences Inc., of South San Francisco, filed an S-1 to raise up to \$70 million in an IPO. The number of shares and share price have not yet been disclosed. Ideaya seeks a Nasdaq listing under the ticker IDYA. Citi and Jefferies are the joint bookrunners. Ideaya is in phase I development, developing targeted therapies for genetically defined cancers.

Mustang Bio Inc., of New York, priced its public offering of about 6.89 million shares at \$4 apiece for gross proceeds of about \$27.5 million. Underwriters have a 30-day option to purchase up to an additional 1 million shares to cover overallocments. Funds will be used to continue development of product candidates, the potential in-licensing, acquisition, development and commercialization of other pharmaceutical products and for general corporate purposes. Cantor Fitzgerald & Co. is acting as lead book-running manager, while Oppenheimer & Co. Inc. is acting as book-running manager, and H.C. Wainwright & Co. and Roth Capital Partners are acting as co-managers for the offering, expected to close May 2. Shares of Mustang (NASDAQ:MBIO) closed Tuesday at \$4.15, down 42 cents.

Novan Inc., of Morrisville, N.C., said it secured up to \$35 million in nondilutive capital to advance its late-stage dermatology assets. Of that, \$25 million is available immediately and \$10 million is contingent upon achieving positive phase III results of SB-206 in molluscum contagiosum. The company plans to begin recruiting patients in May. The product-based financing agreement was inked with Reedy Creek Investments LLC, which is currently Novan's largest shareholder, holding about 15% of outstanding shares. In return for the funding, Reedy Creek will receive 10%, 20% and 20% of any North American economics, including up-front payments, milestones and royalties, received by Novan associated with SB-206 for the treatment of molluscum contagiosum, SB-414 for the treatment of atopic dermatitis and SB-204 for the treatment of acne vulgaris, respectively.

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Biotrinity

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Iain Wilcox, investment advisor at French venture capital firm Seventure Partners. “Many years have been spent trying to unpick these conditions with limited success. The dream is that AI and big data start to shed light on genes and environmental factors,” Wilcox told delegates at Biotrinity 2019.

For now, the problem is that many of the datasets are too small. “You need to measure in the millions of individuals, not the tens of thousands,” said Wilcox. “As an investor, lots of companies are presenting with associative datasets. They are trying to pick out the signals, but we need to know, is it causative, and there is a great lack of detail to show that,” he said.

A further issue is that a lot of datasets are under the control of the investigators and have been scraped together from diverse sources, potentially introducing bias.

It also is important to recognize that even if they are causative, targets thrown up by AI and big data will not be tractable cell surface receptors. “A lot of causative links are probably not going to be druggable,” Wilcox said.

For Jorge Ferrer, chair in genetics and medicine at Imperial College London, a more immediate opportunity lies in using big data to stratify patient populations. “Currently, we are not really modifying the disease, and that’s what is really changing with big data. You can stratify patients according to mechanisms,” he said.

An obvious example is insulin deficiency and insulin resistance, for which Ferrer has identified a panel of genetic markers. “It’s not ready for general consumption yet, but it soon will be,” he said.

At the same time, big data and AI are making it possible to unpick the relative contributions of genetics and lifestyle, to understand an individual’s risk of developing type 2 diabetes. “I realize lifestyle is really central, but despite that, genetics has a large role. Not all obese people get diabetes,” said Ferrer. “Now we are aggregating thousands of genetic markers to get a better idea of risk.”

AI and big data also are opening the way to polypharmacy, in which rather than a number of different drugs, diabetes and its co-morbidities are treated with one molecule that hits more than one pathway.

That will “improve compliance and control costs,” said Jacob Sten Petersen, corporate vice president of stem cell R&D at Novo Nordisk A/S. “There are strong co-morbidities, and that’s what people die from. Type 1 and type 2 diabetes patients die from cardiovascular disease, so we need combined treatments,” he said.

AI drug discovery specialist Exscientia Ltd. is making some headway there, according to Andrew Hopkins, CEO. “AI can explore the chemical universe and can find small molecules that hit two pathways,” he said.

In a collaboration with Sanofi SA, Exscientia has discovered a bispecific small molecule that influences weight loss and insulin secretion. “Starting from co-morbidities and mapping

“*There are statin-size opportunities for the right drug.*”

Andrew Hopkins
CEO, Exscientia



back to the pathways, you can then apply computational [techniques] to find these molecules,” said Hopkins.

The potential exists to build “blockbuster-type” markets based on that approach, Hopkins said. “There are statin-size opportunities for the right drug; all the population would be protected at a low price.”

Lifeomics

AI and big data, in the shape of digital health apps, are starting to have an impact in addressing metabolic disease through modifications in lifestyle.

As Mike Trenell, director of the National Institute of Health Research’s Innovation Observatory at Newcastle University noted that, although there are some who argue obesity is a disease, it has been shown that type 2 diabetes can be reversed with dietary restrictions.

“These are behavior-based [conditions]. We need to catch up on [factoring in] behavior. Digital tools mean we can get the data,” Trenell said.

Wilcock agreed. “Some of the tools we have now in the digital arena are becoming more sophisticated and giving people the [means] to make good choices. It can be as simple as a photo of meal saying it is too big,” Wilcock said. “The big dream is not to give people a drug.”

As an investor, he said he believes people will subscribe to digital health apps if there is the evidence to show they deliver a result. “At the moment, we are talking about toys; in the end, people will pay to insure against becoming ill,” said Wilcock.

For Trenell, “lifeomics” data coming out of digital health apps will trump genomics, proteomics “and all the other ‘omics.” The future of managing metabolic diseases lies in understanding and modifying behavior, he said. “Digital health apps mean we can now get the data on behavior.” ♦

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G1

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the FDA meeting, but Macdonald said he expects the NDA and MAA filings to be in 2020, with a potential launch in 2021.

G1 wants to broaden trilaciclib's value beyond SCLC, and that would include a potential breast cancer regimen and another for gastrointestinal malignancies.

"It's a little different than the traditional development path," Macdonald said.

The market was pleased with the news as G1's stock (NASDAQ:GTHX) closed 15.3% higher. For the year to date, it's up 9.4%.

Analysts liked the news, too. On Tuesday, Cowen Inc. continued to rank the stock to "outperform," noting the worldwide market potential could hit \$1 billion. H.C. Wainwright and Co. upped the ante by projecting potential revenues of \$1.6 billion for trilaciclib in 2026.

In December, G1 announced top-line data showing multilineage myelopreservation benefits in its randomized, double-blind, placebo-controlled phase II trial evaluating trilaciclib in combination with topotecan as a treatment for second- and third-line SCLC. The data demonstrated that trilaciclib reduced clinically relevant consequences of myelosuppression vs. placebo when administered in combination with topotecan. It achieved both primary endpoints after multiplicity adjustment. The trilaciclib arm demonstrated statistically significant reductions in both the duration of grade 4 neutropenia in cycle one (mean eight days vs. two days; adjusted one-sided $p < 0.0001$) and occurrence of grade 4 neutropenia (75.9% vs. 40.6%; adjusted one-sided $p = 0.0160$) compared to the placebo arm.

Trilaciclib could also have potential in combination therapy with checkpoint inhibitors. Late in 2016, G1 inked a deal with Roche Holding AG's Genentech unit to test the drug alongside PD-1/PD-L1 inhibitor Tecentriq (atezolizumab). Last November, top-line data from the phase II trial of trilaciclib in combination with chemotherapy/Tecentriq in first-line SCLC confirmed multilineage myelopreservation benefits. There were statistically significant improvements in both primary endpoints of occurrence of grade 4 neutropenia and duration of grade 4 neutropenia in cycle one. There was also a statistically significant reduction in grade 4 thrombocytopenia and clinically meaningful reduction in red blood cell transfusions. The results showed trilaciclib reduced clinically relevant consequences of myelosuppression vs. placebo when administered in combination with chemotherapy (etoposide and carboplatin) and Tecentriq across three lineages: neutrophils, red blood cells and platelets.

In October, new data from its randomized phase II trial in combination with etoposide/carboplatin for the treatment of first-line SCLC demonstrated clinically meaningful improvements for neutrophil, red blood cell and lymphocyte measures in patients treated with trilaciclib compared to placebo. With regard to lymphocytes, trilaciclib preserved or improved B-cell and T-cell subset counts, including activated CD8-positive cells, and increased CD8-positive/regulatory T-cell and activated CD8-positive/regulatory T-cell ratios in peripheral blood compared to placebo.

G1 was founded in 2008 as G-Zero Therapeutics Inc. and changed its name in 2012 when company execs shifted the strategy from selling intellectual property to pursuing a pipeline of kinase inhibitors. It followed up with funding rounds, including a \$33 million series B in 2015 and a \$50 million series C in 2016.

Two years ago this month, G1 priced an IPO to raise \$105 million to advance lead candidates aimed at inhibiting cyclin-dependent kinases. (See *BioWorld Today*, May 18, 2017).

G1 execs have said they believe it is the only company working on a CDK4/6 inhibitor specifically as a bone marrow chemoprotectant, which differentiates trilaciclib from approved CDK4/6 inhibitors such as Ibrance (palbociclib, Pfizer Inc.), approved in 2015 in combination with letrozole for advanced or metastatic breast cancer, and Kisqali (ribociclib, Novartis AG), cleared by the FDA in early 2017 for use in combination with an aromatase inhibitor in postmenopausal women with HR-positive/HER2-negative advanced or metastatic breast cancer. (See *BioWorld Today*, Feb. 4, 2015, and March 14, 2017.) ♦

Financings

Novus Therapeutics Inc., of Irvine, Calif., said it entered definitive agreements with several institutional and accredited investors for the purchase of about 3.4 million shares of its common stock, at a purchase price per share of \$3.095, in a registered direct offering priced at-the-market. Novus also agreed to issue to the investors unregistered warrants to purchase up to about 6.9 million shares of common stock. Gross proceeds are expected to be about \$10.7 million and will be used to fund expansion of the ongoing phase IIa trial in acute otitis media from 50 to about 140 patients, as well as for working capital and other general corporate purposes. H.C. Wainwright & Co. is acting as exclusive placement agent.

Peloton Therapeutics Inc., of Dallas, filed to raise up to \$115 million in an IPO. The number of shares and share price have not yet been disclosed. Peloton, which is developing drugs for cancer and other conditions, is initially targeting HIF-2alpha, with lead drug PT-2977 set to start phase III testing in metastatic renal cell carcinoma in the second half of this year. The company plans to seek a listing on Nasdaq under the ticker PLTX. J.P. Morgan, Citigroup and Jefferies are acting as bookrunners.

Sunesis Pharmaceuticals Inc., of South San Francisco, said it entered a \$5.5 million loan agreement with Silicon Valley Bank, which will allow the firm to retire its existing loan and defer any principal repayment on the new loan for more than 18 months. The new facility includes interest-only payments through 2020, with principal repayment over 24 months beginning in 2021, as well as a lower interest rate than the previous loan. The loan will be used for the repayment of the company's existing indebtedness.

Xortx Therapeutics Inc., of Calgary, Alberta, said it plans to undertake a nonbrokered financing of up to \$5 million of units priced at 20 cents each, with each unit comprising one common share and one-half common share purchase warrant exercisable at 40 cents each for a one-year term. Proceeds will be used to fund upcoming trials, including a pivotal phase III program testing XRx-008.

Vividion

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pulled off an oversubscribed round with its partner on board. Miralles declined to be specific about the programs but said one is “a large, multidomain adaptor protein. These are notoriously impossible to drug conventionally.” Another is a transcription factor, representing an “extremely fertile” prospect. And the third is an E3 ligase, member of a large family involved in degrading proteins. Each bears “a very strong biological rationale, but they are simply inaccessible,” he said, or have been so far. What’s more, the three programs “are completely independent of each other, and the ones that come behind as well, so there’s no intrinsic risk,” he said. “In many companies, they really pound on one pathway or one target, so everything is connected. If that doesn’t work, it falls like a house of cards.”

San Diego-based Vividion’s approach finds novel pockets on proteins and identifies small-molecule ligands to them, so that strategies such as direct inhibition, allosteric modulation and targeted degradation can be deployed to make the discoveries pay. The firm’s main push has been in oncology and immunology, but the platform offers “enormous breadth and we can go after targets across any aspect of biology,” Miralles said. “It’s completely agnostic to the function of the protein. We can detect interaction between a small molecule and a protein regardless of what the protein is. We can detect an interaction with an enzyme as much as we can with a transcription factor.” Also, the technology can screen all proteins in a cell at the same time. “We don’t need to purify, isolate or express a protein,” he said. “That’s, I would say, one of the special sauces of Vividion. Not only do you know what small molecules interact with the target, but equally important, you know what target interacts with what molecule. Therefore, you understand the selectivity of that molecule across the whole human proteome,” which lets Vividion identify what he calls “golden eggs,” or targets with the most promise.

With Celgene, of Summit, N.J., Vividion is pursuing a handful of small molecules against targets for a range of oncology, inflammatory and neurodegenerative indications. Terms of the arrangement call for four years of work, with Celgene potentially extending the pact for another payment, the amount of which the companies left unspecified. The pair is advancing small molecules that function through the ubiquitin proteasome system, modulating specific protein levels for therapeutic benefit. (See *BioWorld*, March 8, 2018.)

Vividion’s deal with Celgene, deliberately crafted as target-based, left plenty of leeway for Vividion’s own research using the platform. “Outside of those predetermined targets, it’s our space,” Miralles said. About the possibility of more such deals and about dealmaking in general, “you have to be pragmatic,” he said. “You want to keep as your own as much as possible, but what is possible is determined by how you can build an organization. I pay tremendous attention to the culture of the company, making sure that all employees are fully engaged

“
We want to build
a company for the ages.”

Diego Miralles
CEO, Vividion Therapeutics



and have ownership of the programs,” a situation that “establishes limits about how much the company can grow and how rapidly,” he said. The purpose of reaching proof of concept with one or more of the three lead programs is not to find a partner, he added, but to create a value inflection point and raise more money. “We want to build a company for the ages,” he said. “We’re doing what we say.”

Opening the window

Vividion pulled down \$50 million in series A cash at the start of 2017. Founded in 2014, the firm is based on work that started with scientist Ben Cravatt, chair of the Department of Chemical Physiology at The Scripps Research Institute (TSRI), whose efforts focused on getting beyond the conventional target-centric approach that typically nets a limited number of hits and leads. (See *BioWorld*, Feb. 2, 2017.)

Work by Cravatt and his team at TSRI, published in 2013 in *Nature*, demonstrated a method of widening that net by developing a way to find ligands – the binding partners – for proteins previously believed unreachable therapeutically. Using a fragment-based ligand discovery approach, researchers attached those fragments to molecules that bind covalently to the amino acid cysteine. It turned out that the human proteome contains many “ligandable” cysteines, including in proteins not shown previously to interact with small molecules. Cravatt’s efforts led to more research into targets that could be engaged by ligands, and the possible mapping thereof. Chemistry from TSRI scientists Phil Baran and Jin-Quan Yu entered the mix.

Genetic findings have sent increasingly more would-be targets down the pike, Miralles noted, which brought about methods such as gene therapy, cell therapy and nucleic acid approaches. “Small molecules kind of fell behind, and seemed to have reached a plateau of things they could drug – mostly enzymes, receptors and channels,” he said. Vividion aims to change that, and he uses phrases such as “opening the window” and “raising the ceiling” in small-molecule research that could enable global reach vs. biologics.

The series B round was led by Nextech Invest, with participation from new investors BVF Partners, Casdin Capital, Mubadala Ventures, Trinitas Capital, Mirae Asset Capital, Altitude Life Science Ventures and Alexandria Venture Investments. Along with Celgene, other existing investors who joined the round included Arch Venture Partners, Versant Ventures and Cardinal Partners. ♦

MS

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the same way that protein aggregates damage neurons in neurodegenerative diseases.

The findings could change several aspects of the way MS is conceptualized.

For one, Manuel Friesse told *BioWorld*, “previously it was thought that... if we could just dampen down inflammation, everything will be fine.”

Friesse is director of the German Institute of Neuroimmunology and Multiple Sclerosis and the senior author of the paper reporting the findings, which appeared in the April 23, 2019, online issue of *Nature Neuroscience*.

Focusing on inflammation has led to success in treating the relapsing-remitting stage of the disease, where bouts of disease are interspersed with periods where patients experience no or nearly no symptoms.

Most patients, though, still ultimately transition to what is known as secondary progressive MS (SPMS), where there are no longer periods of reprieve.

In progressive MS, progression becomes disconnected from inflammation.

“When inflammation has been present for too long, something is irreversibly set up in the nervous system which then runs independently,” Friesse said.

The work also brings attention to the neuronal aspects of multiple sclerosis, where much of the research has been focused on the myelin sheath, whose destruction is the most spectacular feature of the disorder.

“Conceptually, MS was always called a white matter disease,” Friesse said. “It is also, to the same extent, a gray matter disease.” Neurodegeneration, he said, “is the driver of disability,” and the extent of neurodegeneration a patient has correlates much better with disability than the extent of demyelination, which he described as having “very little correlation” with disability.

In addition to the entrenched notion of MS as a white matter disease, it has been technically challenging to study how neurons react to inflammation, since CNS tissue is a mix of neurons, glial cells and – in the case of inflamed tissue – immune cells.

In the work now published in *Nature Neuroscience*, Friesse and his team used a technique called translating ribosome affinity purification (TRAP) to specifically study the effects of brain inflammation on neurons.

They identified a set of several hundred genes whose expression was changed in neurons under inflammatory conditions. Those genes could be clustered into several functions, and one of those functions was protein degradation – a possible indicator that the neurons were trying to clear protein aggregates.

The team next compared the genes that were up-regulated in the mice to genes known to be up-regulated in human brains with MS, and identified the protein Bassoon as strongly increased in both species.

The identification of Bassoon, Friesse said, was initially a

“Conceptually, MS was always called a white matter disease. It is also, to the same extent, a gray matter disease.”

Manuel Friesse

German Institute of Neuroimmunology and Multiple Sclerosis

big surprise. A presynaptic scaffold protein that regulates neurotransmitter vesicle turnover, it had not been previously linked with MS.

However, Bassoon has several features that are similar to other proteins that aggregate in other neurodegenerative disorders. Bassoon is a large protein, which is naturally a bigger challenge for the degradation machinery to handle.

It also has “long stretches of intrinsically disordered residues,” Friesse said, which do not adopt stable 3D conformations – a characteristic that Bassoon shares with proteins such as amyloid beta, tau, huntingtin and alpha-synuclein.

The team showed that in MS, Bassoon accumulated in the cell bodies of neurons, rather than in its normal working spot in the synapse; and that its overexpression reduced life span in flies, while its knockout was neuroprotective in mice; and that proteasome activation boosted its clearance and was also neuroprotective.

Altogether, Friesse said, the findings looked “very similar to primary neurodegenerative diseases, all of which, these days, are conceptualized as proteinopathies.” In MS, the proteinopathy is triggered by inflammation, not by aging.

One implication of the findings, Friesse said, is that “we need to treat progressive MS differently” from relapsing-remitting MS.

“Starting with anti-inflammatory drugs is one way,” he said, “but maybe only the early forms.”

Therapeutic options for SPMS are much more limited than those for relapsing-remitting disease – though in fairness, much better than they were roughly six weeks ago. At the end of March, the FDA approved both Mayzent (siponimod, Novartis AG), and Mavenclad (cladribine, Merck KGaA) for indications that included SPMS. (See *BioWorld*, April 2, 2019.)

Prior to those two approvals, the only option for SPMS was Novantrone (mitoxantrone concentrate for injection, Amgen Inc.), which was rarely used due to its toxicity.

Not that classifying progressive MS as a neurodegenerative disease necessarily makes the path to treatment any clearer in the near term.

As it has in other mouse models of neurodegeneration, boosting either of the cell’s protein disposal system – the ubiquitin-proteasome system or autophagy – improved outcomes in mice with experimental autoimmune encephalomyelitis.

So far, though, none of those approaches have been successfully translated in the clinic.

“We don’t have anything to really stop neurodegeneration,” Friesse said. “All these targeting approaches are quite difficult – how to get rid of specific protein aggregates... is challenging.” ♦

Medicare

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to address drug pricing,” Rep. John Sarbanes (D-Md.) said Tuesday at a House subcommittee hearing on prescription drug coverage in Medicare Parts B and D. But most of those efforts – including capping out-of-pocket costs, forcing rebates to be passed on to the point of sale, increasing transparency or shifting the burden of who pays – are all downstream efforts that ignore the upstream source of the problem, the prices themselves, he added.

“There’s an increased sense in Congress, on both sides of the aisle, that we have to take some pretty dramatic steps to control the costs and the price setting at that end,” Sarbanes said at the hearing before the Energy and Commerce Subcommittee on Health. The purpose of the hearing was to get the Medicare Payment Advisory Commission’s (MedPAC) take on ways to stem the flood of increasing prices.

One suggestion Sarbanes offered is modeled on a Maryland bill that’s waiting for the governor’s signature. The bill calls for the creation of a state Prescription Drug Affordability Board that would have the authority to review drug cost data submitted by manufacturers and then set an upper limit on prices for specific drugs. Six or seven other states are looking at similar measures, Sarbanes said.

MedPAC Executive Director James Mathews said the independent commission hasn’t taken a position on setting a cap on prices, but he acknowledged a correlation between capping a drug’s price and setting a cap on the rate a price can increase over time – something MedPAC has considered in the form of an inflation rebate.

However, he drew a distinction between the pricing of promising new drugs and continuing price increases for older drugs. “We’ve seen the entry of truly revolutionary blockbuster products on the market that cure things like hepatitis C . . . where the benefits of the medication potentially warrant the prices that the manufacturer is charging,” he said. “But we also see instances . . . where you’ve got products that have been on the market for decades where there’s no real active research and development into increasing the efficacy of these products and yet the prices continue to increase year over year.”

Unwarranted cost increases like that could be checked by a Medicare inflation rebate, Mathews said. Such a rebate is guided by the notion that older drugs are to some extent commodities. “The expectation of commodity prices is that they should go down over time,” he said, noting that with products like computers and wide screen TVs, the technology gets better each year at lower prices.

“The question is why these trends work in reverse for prescription drugs, especially these therapies that . . . are long extant on the market,” Mathews said. At a minimum, setting a limit on annual price increases for drugs would be a step toward moderating the detrimental effects those prices have had on Medicare, he added.

On the table

Sarbanes agreed that an inflation rebate would be “a step in the

“

We’ve seen the entry of truly revolutionary blockbuster products on the market that cure things like hepatitis C . . . where the benefits of the medication potentially warrant the prices. . . .

James Mathews

Executive Director, Medicare Payment Advisory Commission

right direction,” but he wanted to go further. “I think we need to put every option on the table,” he said, as he listed some of those options, including Medicare price negotiations, binding arbitration, “some sort of public auction around the pricing of these drugs and even the notion of regulating these drugs as a utility.”

A proposal that the Trump administration has put on the table would tie the price of Medicare Part B drugs to an international pricing index (IPI). Citing logistics and implementation issues, Mathews advised binding arbitration instead. One of the problems with the IPI proposal is that a drug’s price would be set by the IPI, but then a third-party vendor would have few tools to try to get that price from the manufacturer, he noted.

“Price is one of the major drivers of Medicare spending for drugs,” Mathews testified, but as the U.S. system stands now, Medicare has no control over those prices, especially with Part B drugs. Requiring binding arbitration for certain drugs would force manufacturers to come to the table with their best price, he said.

Acknowledging that arbitration has been used successfully in other markets, such as major league baseball, Rep. Gus Bilirakis (R-Fla.) responded that developing a drug is a lot different than signing a pitcher.

Stomping on step therapy

Another issue several lawmakers returned to throughout the hearing was MedPAC’s support for step therapy as a tool to control Part D prices. Rep. Larry Bucshon (R-Ind.) said step therapy, which forces patients to fail on more affordable drugs before they can be covered for a pricier therapy, is a concept that has waxed and waned in popularity over the 30 years he has practiced as a cardiothoracic surgeon.

“At the end of the day . . . it ultimately doesn’t save any money, because it has the potential to delay therapy,” Bucshon said. He urged MedPAC to look at the long-term impact Medicare’s step therapy policies have on patients and their health.

Another doctor in the House, Rep. Raul Ruiz (D-Calif.), said the problem with step therapy is that it often doesn’t consider patients’ medical history – like whether they’ve already failed on the step 1 treatment under a different plan. Ruiz has introduced the Safe Step Act, which would allow patients to bypass step therapy when their doctor knows the first drugs won’t work for them.

Medicare plans need more flexibility in using price control tools such as price therapy, Mathews said, and they must have

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Polyprox

Continued from page 1

will follow once it conducts additional validation work and establishes in vivo proof of concept for its Polyproxin platform. The company is some ways behind the leaders in the rapidly moving field of redirecting the cell's protein degradation machinery against disease-related targets, but



Laura Itzhaki, founder and chief scientific officer, Polyprox

it has adopted a highly distinctive approach, which could greatly increase the scope of that novel drug discovery paradigm.

The early leaders in Protac (proteolysis targeting chimera) chemistry, most notably New Haven, Conn.-based Arvinas Inc., are focused on developing heterobifunctional small-molecule adaptors that can selectively engage both a protein target and an E3 ubiquitin ligase, which tags the protein of interest for programmed degradation through the ubiquitin-proteasome pathway.



Andrew Sandham, executive chairman, Polyprox

Polyprox, in contrast, is developing protein- and peptide-based approaches that accomplish the same goal. "What we're trying to do is open up target space and open up degradation pathway space," executive chairman Andrew Sandham told *BioWorld*. Small-molecule approaches are constrained at either end of the molecule, he said, in terms of the range of the targets they can bind and the E3 ligases they can engage.

Polyprox aims to exploit the greater target recognition capabilities of proteins and peptides to create a library of binders that will allow for a mix-and-match approach to combining target binders with different E3 ligase recognition moieties. "There are hundreds of E3 ubiquitin ligases," Itzhaki told *BioWorld*. "Small-molecule Protacs can currently only access five or six of those." Her lab has already extended that number into "tens" of ligases, she said.

The company is keeping the details of its initial disease and ligase targets, as well as the protein technologies it is employing to modulate them, under wraps for now. Itzhaki's research has ranged widely over different protein and peptide platforms, including tandem repeat proteins, including ankyrin, heat and ARM repeat proteins, as well as stapled peptides and other constrained peptide formats. The company also has expertise in the intracellular delivery of its Polyproxin molecules, as well as in the pathways and networks that orchestrate intracellular protein degradation. Its initial therapeutic focus is on intractable cancer indications, but it is also interested in pursuing central nervous system applications. It is still three to four years from the clinic, so early work is on validating the technology and

selecting a number of programs for lead optimization. "There is a lot of interest in the space, of course," Sandham said. "We want to generate our own data and then engage with partners."

In addition to Sandham, an experienced company builder and biotechnology investor, the Polyprox team includes its chief operating officer, Kevin Moulder, who has held senior roles in many biotech firms, most recently as chief development officer at the London-based immuno-oncology firm Tusk Therapeutics Ltd., which Roche acquired in a deal worth up to \$760 million. (See *BioWorld*, Oct. 1, 2018.)

Investor and biopharma interest

The head start enjoyed by the early leaders in protein degradation is, Sandham said, not a threat. "I see it as validation." Those firms will, moreover, play an important role in opening up the regulatory pathway for Polyprox.

Although still early stage from a drug development standpoint, the field has attracted substantial levels of investor support and big pharma interest. Arvinas, the early pace-setter in developing Protac drugs, is now valued at about \$1.33 billion following a \$120 million IPO, which it priced last September. It has just moved its first drug candidate, ARV-110, which targets androgen receptor, into a phase I trial in castrate-resistant metastatic prostate cancer. C4 Therapeutics Inc., of Watertown Mass., also looms large in this space.

Earlier this year, it extended an existing deal in cancer with Roche Holding AG, of Basel, Switzerland, and entered a new pact in central nervous system disease with Biogen Inc., of Cambridge, Mass. (See *BioWorld*, Jan. 7, 2019.)

Another contender is Cambridge, Mass.-based Kymera Therapeutics Inc., which closed a \$65 million series B round last November. It recently unveiled preclinical data from its lead drug candidate, KYM-001, a first-in-class oral degrader of interleukin-1 receptor-associated kinase 4 (Irak4) in development for MYD88-mutated lymphoma. (See *BioWorld*, Nov. 14, 2018.)

Last month, Asian-American firm Cullgen Inc., of San Diego, received \$16 million in series A funding to progress a pipeline of targeted protein degraders, based on its USmite (ubiquitin mediated small molecule induced target elimination) platform, in cancer and other indications. Its founders have previously reported on the discovery of small-molecule degraders of anaplastic lymphoma kinase, a receptor tyrosine kinase associated with several oncogenic mechanisms, including overexpression, genetic rearrangement and genetic mutation. (See *BioWorld*, April 3, 2018.)

In addition, big pharma and big biotech has also been active this year – those with declared programs include Cambridge, U.K.-based AstraZeneca plc, Thousand Oaks, Calif.-based Amgen Inc., London-based Glaxosmithkline plc, Roche's Genentech arm, Kenilworth, N.J.-based Merck & Co. Inc., and Basel-based Novartis AG.

Cambridge Innovation Capital plc, RT Capital and Cambridge Enterprise co-led the Polyprox round. ♦

Kerastem

Continued from page 1

Kerastem is a subsidiary of privately held [Bimini Technologies LLC](#), of Solana Beach, Calif.

If Kerastem proceeds to phase III, it will be the first company using stem cell therapy to do so. Currently, the only approved products to address alopecia androgenetica, also known as male and female pattern hair loss, are topical minoxidil for men and women and oral finasteride for men. (See table below.)

Hair grafts are used to restore hair to balding areas in men, but do not work for women who typically have more diffuse hair loss.

The technology

The company obtained the exclusive global rights to the

Celution System for Alopecia, the base Kerastem technology, from Cytori Therapeutics Inc. in 2013 along with the manufacturing and commercialization rights for Puregraft, a fat filtration system used in the Kerastem hair regrowth system and other applications.

Kerastem reported top-line results from the phase II study, called STYLE, which has not been published, in December 2017. The 70-patient randomized, single-blinded, controlled trial included 50 men and 20 women, according to Bradford Conlon, CEO of Kerastem and Bimini Technologies.

The three-step procedure included harvesting adipose (fat tissue) from the abdominal and flank areas of an anesthetized patient. The adipose was divided into two parts. One part was processed using the Puregraft system to produce a purified

See Kerastem, page 10

Alopecia drugs in development

| Drug name | Company (developer) | Description |
|--|--|---------------------------------|
| Phase I | | |
| BPM-31543 (calcitrol) | Topical, small molecule; calcitrol; manipulates gene expression | Berg Pharma LLC |
| Autologous human platelet lysate alone | Cell therapy (phase I/II) | Kasiak Research Pvt. Ltd. |
| Phase II | | |
| ATI-501 | Oral, small molecule; JAK1/JAK3 tyrosine kinase inhibitor | Aclaris Therapeutics Inc. |
| ATI-502 | Topical, small molecule; JAK1/JAK3 tyrosine kinase inhibitor (fast-track) | Aclaris Therapeutics Inc. |
| Breezula (clacoterone) | Topical, small molecule; androgen receptor antagonist | Cassiopea SpA |
| CTP-543 | Oral; deuterium-modified version of JAK1/JAK2 inhibitor ruxolitinib (Incyte Corp.) | Concert Pharmaceuticals Inc. |
| Delgocitinib | Small molecule; JAK tyrosine kinase inhibitor | LEO Pharma A/S |
| ENERGI-F701 | Topical, small molecule; AMP activated protein kinase stimulator | Energenesis Biomedical Co. Ltd. |
| FOL-005 | Biological; osteopontin ligand modulator | Follicum AB |
| HSC-660 | Cell therapy; hair-stimulating complex | Histogen Inc. |
| LY-3009104 (baricitinib) | Small molecule; JAK1/JAK2 inhibitor | Eli Lilly and Co. |
| RCH-01 | Cell therapy; dermal sheath cup cells | Replicell Life Sciences Inc. |
| RegenKit A-PRP | Cell therapy; autologous platelet rich plasma and medical device | Regen Lab |
| Phase III | | |
| SM-04554 | Topical, small molecule; Wnt pathway activator (phase II/III) | Samumed LLC |
| PF-06651600 | Oral JAK3 inhibitor (breakthrough therapy status) (phase II/III) | Pfizer Inc. |
| Dutasteride (Avodart) | Oral, small molecule (approved for benign prostatic hyperplasia) | Glaxosmithkline plc |
| Approved | | |
| Finasteride (Propecia) | Oral, small molecule; 5-alpha-reductase inhibitor (continuing trials) | Merck and Co. Inc. |
| Minoxidil (Rogaine) | Topical, small molecule; potassium channel modulator (continuing trials) | Pharmacia & Upjohn |
| Source: BioWorld and Cortellis | | |

Kerastem

Continued from page 9

autologous fat graft. The second portion was processed to obtain a 5-mL cell suspension of adipose-derived regenerative cells (ADRCs). The affected area of the scalp was then anesthetized and marked. Patients received a subcutaneous scalp injection of purified autologous fat or saline (no fat control) followed by a second injection of purified adipose combined with either high dose (20) or low dose ADRCs (20), a blood saline solution (20) or a saline solution (10).

The company showed a 17% increase in the number of hairs in treated regions in men who received the fat injection followed by the low dose ADRCs compared to baseline at six months, according to the company.

“We designed STYLE to evaluate controls with and without the addition of autologous fat as well as both high and lower doses of ADRCs doses and determined that 500,000 cells per square centimeter resulted in a superior outcome,” said Ken Washenik, the study’s principal investigator.

While the new hair growth mostly remained at 12 months, no new growth occurred, Conlon told *BioWorld*.

“Patients could get multiple treatments, but we didn’t look at that in the study. The treatment uses your own cells to restore hair where you had it,” he added, so additional treatments might be appropriate in areas of subsequent hair loss.

Conlon noted that equal numbers of men and women expressed interest in the trial and that women also saw good results, but that the small number of women who participated in the trial did not enable the company to report outcomes for that group.

“As part of the study, we had to shave the scalp multiple times and females in the trial didn’t want to do that. The good news is that we clearly won’t need people to do that if we get approval,” Conlon said.

The phase II trial followed a published case study of nine individuals who had the Kerastem procedure, which reported a 23% increase in hair growth in patients who had injections of fat plus fat enriched with ADRCs and about an 11% increase in one patient who had fat-only injections.

Based on this study, Kerastem received a CE mark and is working with two distributors in the U.K. and Europe. Conlon said the product launched commercially in the U.K. this quarter. The company entered a partnership with Myungmoon Bio Co. Ltd. in South Korea to commercialize Kerastem in that market.

“With regenerative medicine, there is a regulatory mismatch between countries,” Conlon noted. “The CE mark allows us to sell in some countries, while we still are doing testing in the U.S. We are going through the marketing and regulatory process region by region.”

Phase III

Conlon said Kerastem is looking for a company that will help take its product to market in the U.S. and will partner for the phase III trial.

“

We’re putting together a submission package now and would like to be in front of the FDA this year and hope to start treating participants early next year.

Bradford Conlon
CEO, Kerastem LLC

“Patents have been issued now, and we’d like to move as quickly as possible,” Conlon explained. “We’re putting together a submission package now and would like to be in front of the FDA this year and hope to start treating participants early next year.”

He anticipated the trial would enroll 250 to 350 participants.

“Ideally, we would like to run phase III with just men or do two separate trials,” he said. “The trend for women is just as encouraging, but we may be able to get to trial more quickly with men. It’s a bit of a shame, as the procedure may be more relevant for women as they tolerate liposuction better than men and they currently only have Rogaine and wigs. It’s kind of unfair.”

The trial will use the lower dose identified in the phase II trial compared to controls who will receive saline injections. All study centers will be in the U.S.

“The U.S. is really the hair market,” said Conlon.

According to the company, hair loss affects more than 40 million men and 21 million women in the U.S. alone. Even with relatively few options available, the hair loss industry generates revenues of \$7 billion each year.

Other options

Several other products are already in phase III trials. In previous studies, Glaxosmithkline’s dutasteride showed an increase of 23 new hairs per cm² compared to just four new hairs per cm² for finasteride and a greater reduction in thin hairs.

Samumed LLC is recruiting 625 participants for a phase II/III trial in Turkey of its topical SM-04554. Phase II trials showed that daily treatment for 90 days significantly increased follicle counts, hair counts and hair density at both tested doses, 0.15% and 0.25%.

Pfizer is testing five different doses in its global phase IIb/III study of PF-06651600 for individuals with more than 50% scalp hair loss. The company hopes to recruit 660 participants and report results in early 2021. ♦

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Other news to note

Abeona Therapeutics Inc., of New York, said it reported preclinical data demonstrating that ABO-401, its gene therapy for cystic fibrosis (CF), efficiently delivered a highly expressed, functional copy of human mini-CFTR (hCFTR) to the lung of CF mice and restored CFTR function in human CF patient nasal and bronchial epithelial cells. Data were presented at the American Society of Gene and Cell Therapy meeting in Washington. ABO-401 has a regulatable human mini-CFTR gene that is packaged into one of the company's next-generation AIM library capsids, AAV204. In this and other preclinical studies, ABO-401 restored CFTR expression and chloride conductance in airway epithelia, the main cells of the lung that contribute to CF pathology in humans. Robust expression of AAV204 in the lungs of CF mice was observed and demonstrated that the AAV204 capsid was equally or more efficient at delivering gene expression cassettes to the lung compared to other naturally occurring AAV capsids. Further, the data demonstrated that ABO-401 restored CFTR-specific nasal potential difference in CF mice, and that the ABO-401 gene expression cassette makes a fully processed CFTR.

Allergan plc, of Dublin, and **Editas Medicine Inc.**, of Cambridge, Mass., reported data from an ongoing natural history study of patients with Leber congenital amaurosis 10 at the 6th Annual Retinal Cell and Gene Therapy Innovation Summit in Vancouver, British Columbia. Results from the 21-patient study, which measured baseline characteristics and clinical assessments, including visual acuity and full-field threshold sensitivity changes, was used to design a phase I/II trial of AGN-151587 (EDIT-101), a CRISPR genome editing therapy. The study is scheduled to begin patient screening midyear and begin patient dosing in the second half of 2019.

Amicus Therapeutics Inc., of Cranbury, N.J., said it highlighted initial preclinical data from its adeno-associated viral (AAV) gene therapy program for Pompe disease in mice at the American Society of Gene & Cell Therapy meeting in Washington. The study used a single high dose of AAV in GAA knockout mice with either natural unmodified hGAA (natural hGAA) or an Amicus/Penn-engineered hGAA transgene with a lysosomal-targeting cell receptor binding motif (engineered hGAA), which demonstrated more uniform cellular uptake and lysosomal targeting compared to natural hGAA AAV gene therapy. In the central nervous system, the engineered hGAA AAV gene therapy showed robust glycogen reduction in neuronal cells, suggesting that may be an effective way to address neuronal aspects of Pompe disease. The company is developing AAV gene therapies in collaboration with the gene therapy program of the Perelman School of Medicine at the University of Pennsylvania for Pompe disease, Fabry disease, CDKL5 deficiency disorder and one additional undisclosed rare metabolic disease.

Astrazeneca plc, of Cambridge, U.K., and **BenevolentAI**, of London, said they established a long-term collaboration to use artificial intelligence (AI) and machine learning for the discovery and development of new treatments for chronic kidney disease and idiopathic pulmonary fibrosis. Scientists from the two organizations will work together to combine Astrazeneca's genomics, chemistry and clinical data with BenevolentAI's target identification platform and biomedical knowledge graph

– a network of contextualized scientific data (genes, proteins, diseases and compounds) and the relationship between them.

Auris Medical Holding Ltd., of Hamilton, Bermuda, said its board approved a reverse stock split of its common shares at a ratio of 1-for-20. The reverse stock split is expected to become effective Wednesday and the shares to begin trading on the split-adjusted basis on Nasdaq under the company's existing trading symbol EARS.

Beam Therapeutics Inc., of Cambridge, Mass., disclosed preclinical data from the company's base editing platform at the American Society of Gene and Cell Therapy annual meeting in Washington. In the experiment, the base editor BE4 demonstrated high efficiency multiplex base editing of three cell surface targets in primary human T cells (TRAC, B2M and PD-1), knocking out expression of each gene in 95%, 95% and 88% of cells, respectively, in a single electroporation. Editing each of those genes may be useful in the creation of chimeric antigen receptor T-cell therapies with improved therapeutic properties. Each of the genes was silenced by a single targeted base change (C to T) without the creation of double-strand breaks. As a result, the BE4-treated cells also did not have any measurable translocations (large-scale genomic rearrangements), whereas cells receiving the same three edits with a nuclease did show detectable genomic rearrangements.

Brainstorm-Cell Therapeutics Inc., of New York, expanded its cellular technology platform to include Nurown-derived exosomes for potential development across a broad range of central nervous system disorders. Exosomes are nanosized (30–120 nm), cell-derived vesicles that exhibit stability and may provide enhanced cell-to-cell delivery of bio-active molecules across the blood-brain barrier into difficult-to-reach regions of the brain, the company said, and exosomal cargo provides important regulatory functions for many cell processes, including immunomodulation and neuroprotection.

Caprion Biosciences Inc., of Montreal, acquired **Serametrix Corp.**, of Carlsbad, Calif., a specialized provider of immune monitoring services. Caprion plans to leverage the expertise of Serametrix in the analysis of myeloid-derived suppressor cells, as well as its international operations in the U.S., U.K., Australia and China to expand its global geographic coverage. Terms were not disclosed.

Conatus Pharmaceuticals Inc., of San Diego, disclosed a new publication in *Hepatology Communications* detailing results following seven-day treatment with emricasan, the company's pan-caspase inhibitor, in rats with advanced cirrhosis, including increased portal pressure induced by chronic carbon tetrachloride administration. Portal pressure was significantly reduced in emricasan-treated rats relative to vehicle-treated control animals. Reduced portal pressure was associated with significantly better liver function, reduced liver inflammation and reduced fibrosis. Improvements in expression of markers of liver function, including increased expression of vasodilators and reduced expression of vasoconstrictors, were observed in liver cells isolated from emricasan-treated cirrhotic rats, the company said, and in vitro experiments treating human cirrhotic liver cells with emricasan improved the synthetic capacity of hepatocytes from cirrhotic livers and increased expression of specific markers of liver function.

Other news to note

Eirgenix Inc., of New Taipei City, Taiwan, said it entered a license agreement with global generic and biosimilar drug manufacturer Sandoz AG, a unit of Basel, Switzerland-based **Novartis AG**, granting an exclusive license to Sandoz for commercialization rights to breast cancer biosimilar drug EG-12014 (trastuzumab biosimilar) globally, with the exception of Taiwan and mainland China. Under the terms, Eirgenix will receive an up-front payment, milestone payments and is entitled to receive profit-share payments for sales in the territory. Specific financial terms were not disclosed.

Freeline Therapeutics Ltd., of London, signed a multiyear agreement with **Brammer Bio Inc.**, of Cambridge, Mass., to secure a dedicated AAV manufacturing suite in Brammer's location. The agreement will allow Freeline to meet the commercial demand of the FLT-180a program for hemophilia B. Freeline has now deployed its Icellis-based mammalian cell manufacturing at three separate locations, including Brammer, the Cell and Gene Therapy Catapult outside of London, and at a European contract research organization. Brammer terms were not disclosed.

Fujifilm Diosynth Biotechnologies, part of **Fujifilm Holdings Corp.**, Tokyo, received grant funding of up to £3.625 million (US\$4.727 million) from the Tess Valley Combined Authority to establish a Biocampus in Billingham, U.K. The estimated cost of the Biocampus, which will start with an approximately 42,000-square-foot facility, is estimated to be £12.6 million.

Innovate Biopharmaceuticals Inc., of Raleigh, N.C., reported preclinical results from a 12-week study of its larazotide acetate combined with obeticholic acid in the AMLN-diet Gubra NASH mouse model. The combination produced reductions in plasma total cholesterol ($p < 0.001$), absolute ($p < 0.05$) and relative liver weights ($p < 0.01$), relative ($p < 0.001$) and total liver cholesterol ($p < 0.001$), and relative ($p < 0.01$) and absolute liver triglycerides ($p < 0.001$), when compared to control animals who received vehicle alone. The nonalcoholic fatty liver disease activity score improved in a majority of animals treated with the combination compared to vehicle ($p < 0.001$). The combination improved lobular inflammation ($p < 0.01$) compared to vehicle, while histological steatosis scores trended positively.

Kalvista Pharmaceuticals Inc., of Cambridge, Mass., reported preclinical data for two plasma kallikrein inhibitors, KV-998052 and KV-998054, at the Association for Research in Vision and Ophthalmology Annual Meeting 2019 in Vancouver, British Columbia. In mice with VEGF-stimulated retinal edema, treatment with KV-998054 before VEGF injection resulted in a 59% decrease in VEGF retinal thickening at 24 hours ($p = 0.001$). Treatment with KV-998052 24 hours after VEGF injection accelerated resolution of edema at 72 hours by 83% compared with mice given vehicle ($p = 0.015$). The reduction in retinal thickening occurred in multiple layers, including an 87% decrease in the inner nuclear layer.

Nimble Therapeutics Inc., of Madison, Wis., said it started operating as a standalone business after spinning out from **Roche Holding AG**, of Basel, Switzerland, to commercialize

its chemical synthesis technology for drug discovery and development. The firm also completed a series A financing led by Telegraph Hill Partners. Initially, Nimble will use its chemical synthesis platform, developed at Roche, to accelerate discovery and optimization of macrocyclic peptidomimetics as therapeutics.

Ocular Therapeutix Inc., of Bedford, Mass. and **Mati Therapeutics Inc.**, of Austin, Texas, settled their litigation over whether Ocular's Dextenza (dexamethasone ophthalmic insert) infringed on patents held by Mati. The companies agreed not to sue each other regarding the infringement as it relates to the current FDA approval.

Qpex Biopharma Inc., of San Diego, closed a license agreement with Monash University for the worldwide rights to a portfolio of polymyxin antimicrobials for the treatment of highly drug-resistant gram-negative pathogens.

Rocket Pharmaceuticals Inc., of New York, was awarded a \$6.5 million CLIN2 grant from the California Institute for Regenerative Medicine to support the clinical development of RP-L201, a gene therapy for leukocyte adhesion deficiency-I. The company plans to dose the first patient in a phase I/II study of the treatment in the months ahead.

Sernova Corp., of London, Ontario, is collaborating with the University of British Columbia's Sam Wiseman on the development of a cell therapy-based program for the treatment of hypothyroidism. The project will be funded by a Transplant Venture Grant awarded by the Transplant Research Foundation of British Columbia.

Synlogic Inc., of Cambridge, Mass., reported data showing robust and reproducible lyophilization of its synthetic biotic, SYN-1618, at the 22nd Annual Meeting of the American Society of Gene & Cell Therapy in Washington. The process had minimal impact on cell viability and activity compared to the liquid formulation in terms of consumption of Phe or production of the metabolites trans-cinnamic acid and hippuric acid in an in vitro gut simulation model and in vivo in nonhuman primates as well as in a mouse model of phenylketonuria (PKU). Initial studies showed the drug was stable for more than 90 days at 2-8 degrees C and more than 30 days at room temperature. Synlogic is currently testing a frozen liquid version of the drug in single- and multiple-dose expansion cohorts of patients with PKU in a phase I/IIa study and plans to use a solid formulation of SYN-1618 in the future.

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, said it opened a new research facility in San Diego.

Tessa Therapeutics Pte Ltd., of Singapore, reported preclinical data showing TT-16, its combination immunotherapy integrating CAR T-cell therapy and oncolytic adenovirus expressing immunomodulatory molecules, resulted in durable response in various HER2-positive solid tumor models. Furthermore, binary oncolytic adenovirus (Cad) secreting PD-L1 blocking antibody and activation cytokine IL-12p70 improved the persistence and activity of the HER2-CAR T cells even in advanced disease models showing metastasis similar to those seen in patients. Data were presented at the American Society of Gene & Cell Therapy meeting in Washington.

Other news to note

Trillium Therapeutics Inc., of Toronto, opened an office in Cambridge, Mass., which will house a portion of the company's clinical development team. The company plans to seek FDA guidance in mid-2019 on a proposed pivotal trial of intratumoral TTI-621, which targets CD47, in patients with cutaneous T-cell lymphoma. The company plans to start a study testing the intravenous administration of TTI-621 at higher doses in the third quarter of 2019. The company also noted plans to release data from a study testing a second anti-CD47 product, TTI-622, in late 2019.

Trinetx Inc., of Cambridge, Mass., said the University of Debrecen, in Debrecen, Hungary, joined its global health research network that links pharmaceutical companies and contract research organizations conducting clinical trials with health care organizations.

Verseon Corp., of Fremont, Calif., reported preclinical data on VE-4840, an oral plasma kallikrein inhibitor, at the Association for Research in Vision and Ophthalmology Annual Meeting 2019 in Vancouver, British Columbia. In rats, VE-4840 reduced plasma kallikrein-induced retinal thickening (22.7 μm) after 24 hours compared to vehicle treatment (64.7 μm) ($p=0.0053$). The drug also reduced VEGF-induced retinal thickening (48.6 μm) after 24 hours compared to vehicle treatment (70.2 μm) ($p=0.0055$). VEGF-induced retinal vascular permeability was also reduced in rats treated with VE-4840 (39.58 a.u.) compared to vehicle treatment (26.59 a.u.) ($p=0.0250$).

Medicare

Continued from page 7

a robust appeals process. He suggested exemptions from step therapy when the doctor can document a previous failure, which he defined as a lack of response to the drug.

Ruiz pointed out that some failures are compliance issues, because the regimen for a specific drug might not work for the patient. He asked whether Medicare would give exemptions for that kind of failure.

Mathews responded that Medicare is monitoring the step therapy appeals under Part D and has found that most of the appeals favor the patient.

But appeals take time, especially if the coverage for a specific illness or condition has multiple steps. Time could run out for people with some kinds of cancer if they're denied access to the most effective drug at the beginning of their treatment, Rep. Darren Soto (D-Fla.) said. He suggested a step therapy carveout for cancer – something MedPAC has not recommended.

In her closing remarks, subcommittee Chair Anna Eshoo (D-Calif.) took MedPAC to task for its support of step therapy as a price control tool. She reminded Mathews that in its crunching of the numbers, MedPAC can't ignore the patient. The commission shouldn't be discussing "tools" when patients are dying because they can't get the step 3 drug they need, she said, adding, "We can't ignore that. Nor can MedPAC." ♦

Wondering what you missed in *BioWorld Insight*?

Research paves way for new therapies targeting bipolar disorder

Therapeutic options have remained limited for the treatment of bipolar disorder (BD) where, according to the National Alliance on Mental Illness, about 2.6% of the U.S. population is diagnosed with the condition and nearly 83% of those cases classified as severe. Historically, there has been a lack of biopharma industry investment in neurology/psychiatric conditions. However, there are signs that this situation is changing with exciting new research into the underlying biology of BD paving the way for the discovery of promising therapeutic targets. That has catalyzed a noticeable upswing in investment in research and development and the establishment of strategic partnerships in the field that are helping expand the product pipeline.

Cancer biopharma companies will be moving into the spotlight

Investors will shortly be casting a keen eye on the progress of cancer biopharma companies given that fact that the 2019 American Society of Clinical Oncology (ASCO) annual meeting scheduled to take place in Chicago is only about a month away. Prior to the release of the meeting abstracts, the presenting public companies will also be reporting their first-quarter earnings and business updates. That means there's no shortage of potential stock valuation moving events in the near term, and the BioWorld Cancer index will track the performance of the group during that busy period.

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Earnings

Alimera Sciences Inc., of Atlanta, reported that for the three months ended March 31, consolidated net revenue grew 34% to \$12.9 million, compared to \$9.6 million during the first quarter last year. U.S. net revenue was approximately \$6.8 million during the first quarters of both 2019 and 2018. However, end user demand for its drug, Iluvien for the treatment of diabetic macular edema, which represents units purchased by physicians and pharmacies from the company's distributors, increased 10% in the first quarter of 2019 to 939 units, compared to 851 units in the first quarter of 2018. International net revenue increased 118% to approximately \$6.1 million during the first quarter, compared to approximately \$2.8 million for the same period during 2018. The company reported a net loss of approximately \$2.8 million, compared to a net loss of approximately \$7.7 million for the same period in 2018. As of March 31, Alimera had cash and cash equivalents of approximately \$13.1 million. Alimera shares (NASDAQ:ALIM) rose 1 cent to close Tuesday at 97 cents.

Incyte Corp., of Wilmington, Del., said for the first quarter, net product revenues of Jakafi (ruxolitinib) were \$376 million as compared to \$314 million for the same period in 2018, representing 20% growth. Net product revenues of Iclusig (ponatinib) were \$21 million for the quarter. Ex-U.S. product royalties from sales of Jakavi, which had been out-licensed to **Novartis AG**, of Basel, Switzerland, were \$46 million and \$41 million for the first quarters 2019 and 2018, respectively; royalties from the company's rheumatoid arthritis, drug Olumiant (baricitinib), licensed to **Eli Lilly and Co.**, of Indianapolis, totaled \$16 million compared to \$6 million in the 2018 first quarter. Total revenues amounted to \$498 million

(\$382 million in Q1 2018). Incyte posted net income of \$102 million, or 48 cents per basic and 47 cents per diluted share, as compared to net loss of \$41 million, or 19 cents per basic and diluted share for the same period in 2018. The company had about \$1.6 billion in cash, equivalents and marketable securities at the end of the reporting period. Incyte shares (NASDAQ:INCY) rose \$2.42 on Tuesday to close at \$76.80.

Neurocrine Biosciences Inc., of San Diego, reported that for the quarter ended March 31, total revenue, mainly generated from sales of its drug, Ingrezza (valbenazine), which received FDA approval in 2017 for the treatment of adults with tardive dyskinesia, was \$138.4 million compared to \$71.1 million for the same period in 2018. The company reported a net loss of \$102.1 million, or \$1.12 net loss per share, compared to \$41.8 million, or 47 cents net loss per share, for the same period in 2018. The increase in net loss for the first quarter of 2019 is primarily due to \$113.1 million of in-process research and development (IPR&D) in connection with the strategic collaboration with **Voyager Therapeutics Inc.**, of Cambridge, Mass., to develop and commercialize four experimental adeno-associated virus-based gene therapies, starting with one for Parkinson's disease and another for Friedrich's ataxia. In March, the company made an up-front payment of \$115 million and purchased \$50 million of Voyager's common stock. The company accounted for that transaction, including related transaction costs, as an asset acquisition and expensed \$113.1 million as IPR&D and recorded the \$50 million equity investment at \$54.7 million as an asset on the company's balance sheet based upon the fair value at the time of closing. The company closed the period with cash, cash equivalents and short-term investments of \$524 million. Neurocrine shares (NASDAQ:NBIX) fell \$4.53 on Tuesday to close at \$72.24. (See *BioWorld*, Jan. 30, 2019.)

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Clinical data for April 30, 2019

| Company | Product | Description | Indication | Status |
|---|----------------------------------|---|--|---|
| Phase I | | | | |
| Akcea Therapeutics Inc., of Cambridge, Mass. | AKCEA-APOCIII-LRx | Apolipoprotein C3 antagonist | Cardiovascular disease, hypertriglyceridemia | Results from randomized, double-blind, placebo-controlled, dose-escalation phase I/II study in 67 healthy individuals with elevated triglyceride levels (TGs) and apolipoprotein C-III (apoC-III), published in <i>European Heart Journal</i> , showed dose-dependent reductions of apoC-III protein (up to 84% after 6 weeks) and TGs (up to 71%) in patients with hypertriglyceridemia; AKCEA-APOCIII-LRx also promoted favorable lipid profile by lowering total cholesterol and apolipoprotein B while increasing high-density lipoprotein cholesterol |
| Aptinyx Inc., of Evanston, Ill. | NYX-458 | NMDA receptor modulator | Cognitive impairment associated with Parkinson's disease | Randomized, placebo-controlled study in 62 healthy volunteers evaluating single and multiple ascending oral doses (10 mg to 200 mg) showed favorable safety and tolerability profile with no serious adverse events reported and no adverse events leading to discontinuation |
| Biogen Inc., of Cambridge, Mass. | Spinraza (nusinersen) | Antisense oligonucleotide | Later-onset spinal muscular atrophy | Long-term phase I/II data published in <i>Neurology</i> showed treated individuals with later-onset disease regained motor function previously lost, and treatment stabilized their disease activity, leading to improvements in activities of daily living; subjects with SMA type 2 increased Hammersmith Functional Motor Scale-Expanded scores by 10.8 points, while those with type 3 improved by 1.8 points, vs. a decline of 1.7 points in natural history comparison; all non-ambulant children with type 3 achieved maximum score of 18 points on Upper Limb Module assessment by day 350 and maintained that level of function through day 1,150; type 3 subjects increased distance walked by 92 meters in 6-Minute Walk Test vs. a 1.5-meter decrease in natural history patients in same test after 1 year |
| Cell Medica Ltd., of London | CMD-501 | IL-15 receptor agonist; IL-15 gene stimulator | Neuroblastoma | In children with relapsed/refractory high-risk disease, early data from first 2 patients at lowest dose level (3 x 10 ⁶ CAR-NKT cells/m ²) showed in vivo expansion of CAR-NKT cells and subsequent infiltration of those cells into solid tumor mass and bone marrow; radiological evidence of tumor regression at 4 weeks post infusion in 1 patient, with further regression seen at 8 weeks |
| Cerevance LLC, of Boston | CVN-424 | Modulates D2-dependent indirect pathway | Parkinson's disease | Met primary endpoint of safety in healthy volunteers who received either single doses or 7 daily doses, ranging from 1 mg to 225 mg, or placebo |
| Daiichi Sankyo Co. Ltd., of Tokyo, and AstraZeneca plc, of Cambridge, Mass. | Trastuzumab deruxtecan (DS-8201) | ErbB2 tyrosine kinase receptor inhibitor; topoisomerase I inhibitor | HER2 positive metastatic breast cancer | Long-term efficacy results, reported in <i>Lancet Oncology</i> , for 115 participants who received at least 1 dose, including 111 evaluable for confirmed response, at recommended dose of 5.4 or 6.4 mg/kg in escalation/expansion parts of study showed confirmed objective response rate of 59.5% [95% CI: 49.7-68.7] and disease control rate of 93.7% [95% CI: 87.4-97.4]; median duration of response was 20.7 months (range 0.0-21.8), median progression-free survival was 22.1 months (range 0.8-27.9) and median overall survival was not reached; 55 (48%) remained on treatment at data cutoff of Aug. 10, 2018 |
| Daiichi Sankyo Co. Ltd., of Tokyo, and AstraZeneca plc, of Cambridge, U.K. | Trastuzumab deruxtecan (DS-8201) | ErbB2 tyrosine kinase receptor inhibitor; topoisomerase I inhibitor | HER2-positive advanced gastric or gastroesophageal junction cancer | As reported in <i>Lancet Oncology</i> , long-term data for 44 patients treated at recommended dose of 5.4 or 6.4 mg/kg in escalation/expansion parts of study showed confirmed objective response rate of 43.2% and disease control rate of 79.5%; median duration of response was 7 months (range 4.4-16.6), median progression-free survival was 5.6 months and median overall survival was 12.8 months (range 1.4-25.4); 3 participants remained on treatment at data cutoff of Aug. 10, 2018 |

| Company | Product | Description | Indication | Status |
|---|-------------------------|---|---|--|
| Phase II | | | | |
| Abivax SA, of Paris | ABX-464 | Rev protein modulator | Ulcerative colitis | Canada became first country to authorize design of phase IIb trial expected to enroll first patient this quarter; randomized, double-blind, placebo-controlled, 4-arm, dose-ranging study in 232 participants will evaluate 3 escalating doses (25 mg, 50 mg, 100 mg) vs. placebo; primary endpoint is reduction in modified Mayo Score at 8 weeks; secondary endpoints include clinical remission, endoscopic improvement and biomarker fecal calprotectin; top-line data expected around year-end 2020 |
| Athera Biotechnologies AB, of Stockholm | ATH-3G10 | Phosphorylcholine-targeted monoclonal antibody | Myocardial infarction | First participant enrolled in proof of concept study of MI patients at high risk to develop heart failure; participants will receive a single dose of study drug or placebo; primary endpoint is left ventricular expansion, measured by MRI imaging; initial data expected to report in 2020 |
| Axovant Gene Therapies Ltd., a unit of Axovant Sciences Ltd., of Basel, Switzerland | AXO-Lenti-PD | Dopa decarboxylase stimulator; GTP cyclohydrolase-I stimulator; tyrosine hydroxylase stimulator | Parkinson's disease | First participant enrolled in second cohort of SUNRISE-PD trial that will include up to 6 patients dosed at 1.4 x 10 ⁷ TU; primary outcome measure is safety and tolerability, with key efficacy measure of UPDRS part III (motor) OFF score; initial data from cohort expected in fourth quarter of 2019 |
| Biovie Inc., of Los Angeles | BIV-201 (terlipressin) | Vasopressin V1 receptor agonist | Ascites | Top-line data from open-label phase IIa study in 6 participants met primary objectives; continuous infusion through portable infusion pump was maintained for 28 days in 3 patients with refractory ascites who remained hemodynamically stable; steady state plasma concentration data showed pharmacokinetics fell within predicted model; 4 of 6 patients treated with study drug showed increase in number of days between paracenteses, ranging from 71% to 414%, compared to baseline |
| Hemispherx Biopharma Inc., of Ocala, Fla. | Ampligen (rintatolimod) | Toll-like receptor 3 modulator | Ovarian cancer | Investigator-sponsored trial at University of Pittsburgh Medical Center is accruing participants to evaluate study drug in combination with Keytruda (pembrolizumab, Merck & Co. Inc.) in advanced recurrent disease |
| Medicenna Therapeutics Corp., of Toronto | MDNA-55 | IL-4 receptor modulator" | Recurrent glioblastoma | Completed enrollment of phase IIb study; company is evaluating data from 25 individuals treated at high dose to assess survival outcomes and tumor response, with interim top-line results expected this quarter |
| Myokardia Inc., of South San Francisco | Mavacamten | Myosin inhibitor | Obstructive hypertrophic cardiomyopathy | Results from PIONEER-HCM study, published in <i>Annals of Internal Medicine</i> , showed treatment of 21 participants for 12 weeks resulted in improvements across primary and secondary endpoints; mavacamten could be dosed to eliminate left ventricular outflow tract pressure gradient below guideline-based definition of obstruction (30 mmHg) or below level used to recommend invasive intervention (50 mmHg); participants also showed improvements in New York Heart Association functional classification and exercise capacity as measured by peak VO ₂ levels; reductions in shortness of breath and in levels of NT-proBNP, a marker of ventricular wall stress, also seen |
| Oncology Venture A/S, of Hørsholm, Denmark | 2X-121 | PARP 1/2 inhibitor | Advanced ovarian cancer | First patient dosed in study employing company's Drug Response Predictor to find best responding patients; 30 participants expected to be enrolled, with complete or partial remission rates as primary efficacy endpoint |
| Phase III | | | | |
| Aldeyra Therapeutics Inc., of Lexington, Mass. | Reproxalap | Aldehyde-binding small molecule | Noninfectious anterior uveitis | Last patient completed dosing in Solace trial; results expected in second half of 2019 |

| Company | Product | Description | Indication | Status |
|--|--|---|---|---|
| Intec Pharma Ltd., of Jerusalem | Accordion Pill Carbidopa/ Levodopa | Combination treatment given via gastric-retentive delivery technology | Advanced Parkinson's disease | Last patient completed the final visit in pivotal Accordance trial vs. immediate-release CD/LD (Sinemet); top-line results expected in July/August 2019 |
| Morphosys AG, of Planegg/Munich, Germany, and I-Mab Biopharma Co. Ltd., of Shanghai | MOR-202/ TJ-202 | CD38 antibody | Relapsed or refractory multiple myeloma | First patient dosed in study testing drug in combination with lenalidomide |
| Notes For more information about individual companies and/or products, see Cortellis . | | | | |

Regulatory actions for April 30, 2019

| Company | Product | Description | Indication | Status |
|--|-----------------------------------|---|---|--|
| Abbvie Inc., of North Chicago | Skyrizi (risankizumab) | IL-23-inhibiting monoclonal antibody | Moderate to severe plaque psoriasis | Approved by European Commission for use in adults who are candidates for systemic therapy |
| Dynacure SAS, of Strasbourg, France | DYN-101 | Antisense drug designed to modulate expression of dynamin 2 | Centronuclear myopathies | U.K.'s Medicine and Healthcare products Regulatory Agency approved the clinical trial application for a phase I/II study, Unite-CNM, to start in the second half of 2019 |
| G1 Therapeutics Inc., of Research Triangle Park, N.C. | Trilaciclib | Myelopreservation agent | Protect bone marrow from damage by chemotherapy | Based on written feedback from end-of-phase II meeting with FDA and discussions with European regulators, company plans to submit marketing applications in U.S. and Europe for use in small-cell lung cancer; plans to request pre-NDA meeting with FDA in the fourth quarter of 2019 |
| Janssen Pharmaceutical Cos., of Raritan, N.J., part of Johnson & Johnson | Erleada (apalutamide) | Androgen receptor inhibitor | Metastatic castration-sensitive prostate cancer | Submitted supplemental NDA to the FDA; application being reviewed through real-time oncology review program |
| Mayne Pharma Group Ltd., of Adelaide, Australia | Halobetasol propionate foam 0.05% | Topical corticosteroid | Plaque psoriasis | FDA approved trade name Lexette; product approved in U.S. in May 2018 |
| Phoenix Tissue Repair Inc., of Boston | PTR-01 | Protein replacement therapy | Recessive dystrophic epidermolysis bullosa | FDA granted fast track designation |
| Vertex Pharmaceuticals Inc., of Boston | Kalydeco (ivacaftor) | CFTR potentiator | Cystic fibrosis | FDA approved for use in children, ages 6 months to less than 12 months who have at least 1 mutation in CFTR gene that is responsive to Kalydeco based on clinical and/or in vitro assay data |
| Xencor Inc., of Monrovia, Calif. | XmAb-14045 | CD123 x CD3 bispecific antibody molecule | Relapsed or refractory acute myeloid leukemia and other CD123-expressing hematologic malignancies | FDA lifted partial clinical hold placed on phase I trial following discussion and agreement with agency on amendments to protocol, including guidance on the monitoring and clinical management of cytokine release syndrome |
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