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$335M INVESTMENT

Bayer and Crispr Therapeutics ink alliance targeting genetic diseases

By Peter Winter, BioWorld Insight Editor

It has been a hectic year for Crispr Therapeutics AG, which is ending with a flourish following the announcement that Leverkusen, Germany-based Bayer AG is investing a total of $335 million in order to establish a long-term alliance that will leverage promising CRISPR-Cas9 gene-editing technology.

The deal follows the Basel, Switzerland-based company, which holds the CRISPR-Cas9 patent estate for human therapeutic use from its scientific co-founder Emmanuelle Charpentier, inking a four-year collaboration with Vertex

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Lilly looks to Halozyme delivery technology in potential $825M deal

By Michael Fitzhugh, Staff Writer

Halozyme Therapeutics Inc. added Eli Lilly and Co. to the roster of companies angling to develop products incorporating its Enhanze delivery platform, a potential aid in the dispersion and absorption of its injectables. The deal includes $25 million up front and up to $160 million for each of up to five

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DEALS AND M&A

Tivo replay: EU deal affirms near-term plan for Aveo in RCC

By Jennifer Boggs, Managing Editor

Aveo Oncology Inc. signed up specialty cancer firm Eusa Pharma Ltd. as its European partner for its VEGF tyrosine kinase inhibitor, tivozanib, in a deal that helps validate the biotech's continued

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FINANCINGS

Diurnal raises $44.7M, lists on AIM, awaits Infacort phase III readout in 3Q16

By Nuala Moran, Staff Writer

LONDON – Diurnal plc has raised £30 million (US$44.7 million) in a listing on the Alternative Investment Market (AIM) in London and a convertible loan, enabling it to complete phase III

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DEALS AND M&A

Medigene grabs a piece of Amgen's Imlygic in IP licensing deal

By Cormac Sheridan, Staff Writer

DUBLIN – Medigene AG is getting a slice of the action from sales of Amgen Inc.'s pioneering oncolytic virus therapy Imlygic (talimogene laherparepvec), in an intellectual property licensing deal

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Brain balance mechanism key to neurology treatments

By John Fox, Staff Writer

HONG KONG – Japanese and French researchers have discovered the cellular signaling mechanism whereby the balance of disturbed inhibitory

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BIOSIMILARS

Biosimilars unlikely to impact poorer markets

By Cornelia Zou and Alfred Romann, Staff Writers

HONG KONG – Fear of biosimilars, drugs that once launched will potentially capture entire markets with their discounted prices, is not likely to be an issue in some of the poorer countries in Asia and Latin America, where even

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FINANCINGS

Aquinnah Pharmaceuticals Inc., of Cambridge, Mass., said it received a $5 million investment from **Takeda Pharmaceutical Co. Ltd.**, of Osaka, Japan, in a private equity financing. The company is targeting pathological protein complexes found in the brain of the majority of patients with amyotrophic lateral sclerosis (ALS). It has designed its newly identified compounds to slow or reverse the progression of ALS by attacking and breaking down those protein complexes, with the goal of swiftly moving a new class of ALS drugs into clinical development.

Checkpoint Therapeutics Inc., of New York, said it closed on a total of $58 million in a series of private placement financings involving the sale of units, each consisting of 10,000 shares of common stock and a warrant exercisable for 2,500 shares of common stock at an exercise price of $7 per share, for a purchase price of $50,000 per unit. The warrants have a five-year term and are only exercisable for cash. The company is focused on the acquisition, development and commercialization of nonchemotherapy, immune-enhanced combination treatments for patients with solid tumor cancers.

Immunome Inc., of Philadelphia, said it raised $5 million in a series A preferred stock financing, with $3.6 million funded and $1.4 million committed and expected to close in the near future. The company anticipates using proceeds to fund further development of its pipeline of cancer therapeutic antibodies stemming from its RealMab platform. The financing included investments from new and existing investors. Broadband Capital Management acted as exclusive placement agent.

Nuo Therapeutics Inc., of Gaithersburg, Md., said the company entered a third limited consent with Deerfield Management LP to modify certain provisions of its credit facility agreement. For the period between Dec. 18, 2015, and Jan. 7, 2016, the amount of cash that Nuo is required to maintain in a deposit account subject to control agreements in favor of the Deerfield lenders has been reduced from $5 million to $500,000; and the date for the company's payment of the accrued interest amount, originally payable on Oct. 1, has been extended to Jan. 7, 2016. In addition, Nuo is required to continue to engage a representative of Winter Harbor LLC as its chief restructuring officer and to provide Deerfield with copies of certain contacts, agreements and vendor relationships by Dec. 28; or the limited consent will no longer be effective and Nuo will be in default of the facility agreement. The purpose of this third limited consent is to allow Nuo an opportunity to complete its preparations for seeking court supervised protection from creditor claims or for a restructuring.

STOCK MOVERS 12/21/2015

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$26.34	+0.76%
Adamas Pharmaceuticals	+$1.73	+11.73%
Aegerion Pharmaceuticals	+$1.40	+15.54%
Agios Pharmaceuticals Inc.	+$7.99	+14.15%
Novabay Pharmaceuticals	+$1.04	+40.51%

Biotechs showing significant stock changes Monday

OTHER NEWS TO NOTE

Antibiotx ApS, of Hoersholm, Denmark, initiated a preclinical study to determine the repeat-dose tolerability of the ATx201, its topical treatment for bacterial skin infections. The objective of the study is to evaluate the potential dermal toxicity of ATx201 after it has been administered topically twice daily for 28 days, followed by another 28-day recovery period. The study will be conducted on 26 Hanford miniature swine.

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Crispr

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Pharmaceuticals Inc. in late October to discover and develop treatments for genetic diseases, including cystic fibrosis and sickle cell disease. (See *BioWorld Today*, Oct. 27, 2015.)

That collaboration provides Crispr with $105 million up front, including $75 million in cash and a $30 million equity investment. In return, Boston-based Vertex received the option to an exclusive license for up to six gene-based treatments that emerge from the collaboration.

With Bayer, a joint venture (JV) will be formed involving a newly established Bayer Lifescience Center (BLSC), which operates as a strategic innovation unit in Bayer that reports directly to Bayer's board of management. Crispr will be contributing its CRISPR-Cas9 gene-editing technology and intellectual property to the venture, with Bayer making available its protein engineering expertise and relevant disease know-how.

Rodger Novak, CEO and co-founder of Crispr Therapeutics, told *BioWorld Today* that the JV would be transformative for the company because it now has the support of a big pharma to augment research on systemic delivery technologies.

Under the terms of the long-term JV, which will shortly receive an official name and be located in London, with operations also in Cambridge, Mass., Bayer will provide a minimum investment of $300 million in research and development over the next five years. In addition, Bayer will acquire a minority stake in Crispr Therapeutics for $35 million in cash. The JV will be led by Axel Bouchon, head of the BLSC, on an interim basis as CEO, while Novak will serve as the interim chairman of a newly formed JV board.

"The deal provides us access to the world-class protein engineering resources developed within Bayer," added Novak. "It is also a very focused initiative targeting conditions in hematology, ophthalmology and regenerative medicine cardiology. On top of that, we are able to retain a 50 percent ownership of the development of any potential therapies and new technologies targeting serious genetic conditions in these three areas."

In addition, the company will retain full access to target delivery technologies and intellectual property development by the JV, which can then be leveraged to support the company's own internal programs.

Newly created know-how from the collaboration around the CRISPR-Cas9 system beyond the three disease areas, will be exclusively made available to Crispr for human use, and to Bayer for nonhuman use such as agricultural applications.

Bayer may also secure exclusive rights to use Crispr's and the JV's technology and intellectual property in the three targeted disease areas, including blood disorders, blindness and congenital heart diseases. In addition, Crispr may gain exclusive access to Bayer's protein engineering know-how for use in its products as well as Bayer's extensive expertise and knowledge in the three targeted disease areas. All technology development and future IP developed by the JV will also be exclusively available to both companies.

In order for the company to maintain its focus on its own internal programs and what it needs to achieve going forward, Novak noted that Crispr intends to hire a new team for the JV, as there will be a very limited number of people from each company joining the new venture.

The transaction is expected to close in the first quarter of next year. //

IN THE CLINIC

Abivax SA, of Paris, completed patient enrollment in its ongoing phase IIa study of ABX464-003. The randomized, double-blind, placebo-controlled phase IIa monotherapy dose-ranging study involves HIV-infected patients in Mauritius and in Thailand who have never received antiviral drugs. Patients in the 25-mg, 50-mg, 75-mg, 100-mg and 150-mg dose cohorts were administered the drug-candidate orally once daily for three weeks. Each dose cohort consists of six patients treated with ABX464 and two patients receiving placebo. The primary endpoint is to evaluate the safety and tolerability of ABX464 after repeated oral administrations of five different doses. Secondary endpoints will examine its pharmacokinetic profile and its impact as a monotherapy on the viral load.

Achelios Therapeutics Inc., of Chapel Hill, N.C., reported phase IIa data showing that the application of Topofen, the firm's formulation of a nonsteroidal anti-inflammatory drug, on the skin, over the trigeminal nerve branches in the temple and neck area of the face, appear to be a safe and effective alternative treatment for patients suffering from acute migraine. Compared with placebo, Topofen resulted in greater improvement in pain assessments after study drug application, a faster time to pain response, a reduction of migraine-associated symptoms such as nausea, light and sound hypersensitivity and greater suppression of pain over a 24-hour period. Of the severe migraine patients, 45 percent had sustained pain relief from two hours to 24 hours, compared to 15 percent of placebo. Fifty percent of patients who treated their severe pain with Topofen were pain-free at 24 hours, compared to 25 percent of placebo-treated patients.

OTHER NEWS TO NOTE

Array Biopharma Inc., of Boulder, Colo., reported the closing of its definitive agreement with Paris-based **Pierre Fabre SA** following approval of the agreement by the European Commission on Competition. The definitive agreement, announced Nov. 16, relates to globally developing and commercializing Array's late-stage oncology products binimetinib and encorafenib. Binimetinib, a MEK inhibitor, and encorafenib, a BRAF inhibitor, are currently advancing in three, global phase III trials for melanoma and ovarian cancer. (See *BioWorld Today*, Nov. 17, 2015.)

Halozyme

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collaboration targets.

Each payment is subject to Lilly's achievement of specified development, regulatory and sales-based milestones. In addition, Lilly will pay Halozyme mid-single-digit royalties if products under the collaboration are commercialized.

The deal fortifies Halozyme's already-brisk Enhanze licensing business, something that Halozyme President and CEO Helen Torley told *BioWorld Today* is a core pillar of the company's business and an important element in funding the ongoing development of its lead oncology candidate, PEGPH20.

The company already has licensing deals in place with Roche AG, Baxalta Inc., Abbvie Inc., Janssen Biotech Inc. and Pfizer Inc., with the latter two currently in the clinic with candidates: Janssen with its blood cancer drug, daratumumab, and Pfizer with the sickle cell candidate rivipansel. (See *BioWorld Today*, Dec. 18, 2014, and June 4, 2015.)

Enhanze is based on Halozyme's recombinant human hyaluronidase enzyme (rHuPH20), which temporarily degrades hyaluronan, a chain of natural sugars in the body, to aid in the dispersion and absorption of other injected therapeutic drugs.

Enhanze can also help enable reduced dosing frequency, something that Torley pointed out has already been demonstrated with Baxalta's Hyqvia (immune globulin infusion 10 percent [human] with recombinant human hyaluronidase) and has been discussed by Pfizer as a potential point of differentiation for its proprotein convertase subtilisin/kexin type 9, or PCSK9, inhibitor, bococizumab.

For Lilly, Halozyme said the technology may allow for more rapid delivery of injectable medications through subcutaneous delivery. But, beyond that, Divakar Ramakrishnan, Lilly's vice president of delivery and device R&D, shared little in commenting on the deal, noting only that Enhanze would "provide a platform for our scientists to optimize delivery of Lilly medicines through subcutaneous injection."

Though not addressed in the announcement, another potential avenue Lilly could also explore is co-formulating rHuPH20 with its products, something that, were it to lead to a new application for an existing medicine, could help it secure additional patent life.

As the year winds down, San Diego-based Halozyme is continuing to ramp up its business, announcing in November that it opened a new satellite office in South San Francisco intended to ease the recruitment of new drug development talent to back its oncology program.

Already, Torley said, the company has added a head of regulatory affairs and safety. "We've drawn the talent from leading companies in San Francisco and we didn't have a long time delay as we waited to see if people could move the entire family down to San Diego," she said. "It's a very pragmatic solution." //

OTHER NEWS TO NOTE

Boehringer Ingelheim GmbH, of Ingelheim, Germany, said the FDA granted breakthrough therapy designation for its third-generation epidermal growth factor receptor (EGFR) mutation-specific tyrosine kinase inhibitor, BI 1482694 (HM61713), in EGFR mutation-positive lung cancer.

Cantabio Pharmaceuticals Inc., of Palo Alto, Calif., completed a reverse merger with **Gardedam Therapeutics Inc.**, also of Palo Alto. Cantabio will have an exclusive focus on the discovery and development of Gardedam's drug pipeline for neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. As part of its portfolio, Cantabio will first progress its research into the DJ-1 protein, advancing small-molecule pharmacological chaperones and engineered blood-brain penetrant DJ-1 drug candidates into preclinical development for the treatment of Parkinson's and Alzheimer's. Cantabio issued 15.5 million shares of its common stock to the holders of Gardedam common stock. Under the terms of the merger, those shares will be restricted from trading for a period of one year from the closing of the merger. After the close, a total of 27.25 million shares of common stock will be outstanding.

Capnia Inc., of Redwood City, Calif., said the FDA designated its nasal CO2 (non-inhaled carbon dioxide) technology an orphan drug to treat trigeminal neuralgia. The company's technology delivers a low-flow rate of CO2 into the nasal cavity and targets local trigeminal nerve endings.

Celgene Corp., of Summit, N.J., said Revlimid (lenalidomide) was granted full marketing authorization by Japan's Ministry of Health, Labour and Welfare to be used in combination with dexamethasone in newly diagnosed multiple myeloma. The authorization expands the 2010 approval of Revlimid for those with relapsed or refractory multiple myeloma. The marketing authorization was based on data from a phase III trial, the FIRST trial (MM-020/IFM 07-01), as well as a confirmatory Japanese phase II study (MM-025).

Coherus Biosciences Inc., of Redwood City, Calif., said it entered a manufacturing agreement with **KBI Biopharma Inc.**, of Durham, N.C., for long-term manufacturing of CHS-1701, Coherus' Neulasta (pegfilgrastim, Amgen Inc.) biosimilar candidate. Under the terms, KBI will manufacture and deliver the necessary amounts of the product for a planned commercial launch and multiple years to supply CHS-1701 for sales. Coherus said it anticipates filing a biologics license application in the second quarter of 2016. No financial details were disclosed.

CSL Behring, of King of Prussia, Pa., said it submitted a new drug application to Japan's Pharmaceuticals and Medical Devices Agency for rIX-FP, CSL's investigational fusion protein linking recombinant coagulation factor IX with recombinant albumin. RIX-FP is a long-acting recombinant albumin fusion protein for those with hemophilia B. The application is based on the PROLONG-9FP clinical program, which studied those with hemophilia B who are ages 1 to 61 years.

Aveo

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push for the beleaguered cancer drug, which might finally be approaching the finish line, at least in Europe.

While the up-front payment is minimal – $2.5 million – the arrangement carries up to $394 million in potential milestones. Of those, up to $37 million are tied to regulatory and reimbursement approvals, offering relatively near-term payouts. Eusa plans to submit a marketing authorization application in renal cell carcinoma (RCC) in the first quarter of 2016.

Up to $22 million in milestones will be tied to additional research and development reimbursement, related to tivozanib studies in refractory RCC and in combination with PD-1 inhibitors, Aveo President and CEO Michael Bailey told investors on an early Monday conference call. Up to $335 million is tied to sales milestones. Aveo also is entitled to tiered royalties ranging from the low double digits up to mid-20 percent range. Aveo will owe sublicensing fees to Tokyo-based Kyowa Hakko Kirin Co. Ltd., which still retains Asia rights to the drug.

"The agreement sets in place one of the last puzzle pieces" of Aveo's tivozanib strategy, set out at the start of 2015, Bailey explained.

Aveo kicked off the year with deep cuts to its staff, slashing two-thirds of its work force, largely comprising its internal research efforts, and later moving to a smaller headquarters in Cambridge, Mass. Meanwhile, the firm has looked for ways to monetize both tivozanib, or tivo, as well as other parts of its pipeline to pad its balance sheet. It inked an option agreement with Ophthotech Inc. for development of tivo in non-oncology eye diseases and licensed rights to tivo to Moscow-based Pharmstandard International SA for Russia, Ukraine and the Commonwealth of Independent States.

Those deals, plus the Eusa transaction, provided nearly $5 million in up-front and research payments, with more than $35 million in potential milestone payments "over the next 18 months alone," Bailey said. On top of that, Aveo has potential milestones coming from its August agreement with Novartis AG, in which it handed over development and commercialization rights to preclinical-stage growth differentiation factor 15-targeting antibody AV-380 in exchange for $15 million up front and up to $326 million in milestones. (See *BioWorld Today*, Aug. 18, 2015.)

Aveo retains rights to tivo in North America. The expected payments over the next year and a half "provide additional support for our planned third-line phase III renal cell carcinoma pivotal study, a key component of our U.S. registrational strategy," Bailey said. In a best-case scenario, data from the roughly 300-patient trial, if positive, could be added to the previous TIVO-1 study and might be "sufficient to support first-line approval, subject to the outcomes of the FDA review."

Results from TIVO-1 demonstrated superiority over Nexavar (sorafenib, Onyx) in advanced RCC, meeting the primary endpoint of progression-free survival (PFS) (11.9 months vs. 9.1 months). In treatment-naïve patients, who represented about 70 percent of the study population, the difference was more pronounced, with tivozanib demonstrating a median PFS of 12.7 months compared to a median PFS of 9.1 months for sorafenib. (See *BioWorld Today*, Jan. 4, 2012.)

Those positive PFS data, however, were blighted by inconsistent overall survival data from TIVO-1, which was attributed at least partially to the trial's complicated crossover design. But it was enough to earn a complete response letter (CRL) from the FDA in RCC, with the agency requesting an additional trial. (See *BioWorld Today*, June 11, 2013.)

TURNING THE STORY AROUND

Designed as a selective inhibitor of VEGFR1, 2 and 3, with a long half-life, tivo is being positioned by Aveo as a differentiated tyrosine kinase inhibitor that can work as a single agent and in combination. But only a year ago, its prospects were looking grim. In addition to the CRL in RCC, Aveo also reported a failed colorectal cancer study with tivo, while a phase II study testing the drug in triple-negative breast cancer was halted due to low enrollment. Soon after, its then-partner Astellas Pharma Inc., of Tokyo, backed out of the tivo deal. The agreement had brought $125 million up front in 2011 and offered potential milestones topping $1 billion. (See *BioWorld Today*, Feb. 18, 2014.)

Aveo forged ahead with tivo, despite those setbacks, streamlining operations to focus solely on near-term opportunities for the drug.

"Looking to 2016 and beyond, I hope to see several milestones to help move Aveo forward," Bailey said. Those include potential milestones from Ophthotech in ophthalmology settings and Russian filing announcements from Pharmstandard.

In Europe, too, the path to approval for new partner Eusa is expected to be more straightforward. "We are encouraged by the support of the rapporteur and co-rapporteur," Bailey added. The deal with Eusa, a company that launched earlier this year after acquiring specialty products from Jazz Pharmaceuticals plc, affirmed that optimism. Shares of Aveo (NASDAQ:AVEO) closed Monday at $1.26, up 23 cents, or 22.3 percent.

"You really are turning the Aveo story around," noted Piper Jaffray analyst Ted Tenthoff on the call.

Aveo plans to start its third-line RCC study in the second quarter of next year. Combined first- and third-line RCC represents a "high-value opportunity, with the U.S. renal cell carcinoma market currently accounting for more than $1 billion in sales," Bailey said. And the advent of checkpoint inhibitors is expected to make that opportunity even more attractive. "We believe the long-term survival conveyed by the checkpoint inhibitors in second-line may expand the third-line market," increasing the chances for patients to receive more lines of therapy.

Aveo also isn't finished with tivo in colorectal cancer. Bailey said

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Diurnal

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development of two products based on its modified release version of hydrocortisone for treating congenital adrenal hyperplasia and adrenal insufficiency.

This is a big step up for the company, which previously had raised a little short of £10 million since it was spun out of Sheffield University in 2004. "We have done something rare in the U.K., which is to take two products from concept to late-stage clinical trials, and on a modest budget to date," Martin Whitaker, CEO, told *BioWorld Today*.

Diurnal has placed 17.6 million shares at £1.44 per share with new and existing investors, raising gross proceeds of approximately £25.3 million. In addition, its majority shareholder IP Group plc is making a five-year, interest-free convertible loan of $4.7 million.

While taking the company public is not an exit for the venture capital backers, Whitaker said the company "had thought about it very carefully" and decided the listing would be the best way to raise more capital in the future. The decision follows the recent appointment of U.K. biotech veteran Peter Allen, as chairman.

The company's two products, Chronocort for adults and Infacort for children, are formulated to have the same release profile as cortisol, thereby providing better control of the symptoms arising from congenital adrenal hyperplasia and adrenal insufficiency. The production of the natural hormone, which is essential for maintaining energy metabolism, growth and fertility, increases overnight to reach a peak in the early morning.

Chronocort mimics this circadian rhythm by using a microparticulate formulation that allows for sustained release of hydrocortisone and by a "toothbrush" dosing regimen in which a higher dose of the oral formulation is taken at bedtime and a lower dose on waking.

Infacort is intended to be used in children between 0-6 years, an age range when the shortcomings of existing replacement therapy with hydrocortisone are particularly marked. Currently, there is no licensed pediatric therapy.

Development of Infacort, which recently entered phase III, has received €5.6 million (US$6.1 million) grant funding from the European Union. The results of the trial are expected in the third quarter of 2016, with approval expected in 2017.

Meanwhile, Whitaker said Chronocort is due to enter phase III at the start of the new year. Phase II development of the product was carried out under a U.S. National Institutes of Health Cooperative Research and Development Agreement. The 16-patient trial met its primary endpoint of "acceptable pharmacokinetics" and levels of associated biomarkers, including androgens, 17-hydroxyprogesterone and androstenedione, were restored to optimal levels during the six-month study.

Both Chronocort and Infacort have orphan designations in the U.S. and Europe. According to Cardiff-based Diurnal, some 250,000 people worldwide have congenital adrenal hyperplasia or adrenal insufficiency. The condition is poorly controlled on existing therapies. Common symptoms arising from too little hydrocortisone are tiredness, nausea and weight loss.

Diurnal is built on the research of Richard Ross, professor of endocrinology at Sheffield University, whose investigation of the health of congenital adrenal hyperplasia patients at 17 centers in the U.K. highlighted the inadequacy of existing therapies.

In 2004, Ross demonstrated the short plasma half-life of current hydrocortisone replacement therapy makes it impossible to replicate the overnight rise in cortisol levels that occurs naturally and that this is the main cause of poor control of the condition.

Without appropriate cortisol replacement at night, androgen precursor hormones accumulate and can cause precocious puberty, infertility and virilization in women. To try and prevent this overnight rise in androgens, clinicians often overtreat patients with steroids, leading to obesity and reduced bone density.

Ross demonstrated that continuous intravenous infusion of hydrocortisone made it possible to replicate the overnight cortisol rise and the circadian rhythm, and that this improved disease control. He subsequently developed the Chronocort oral modified-release formulation.

The company's foundations in Ross' work and its involvement in EU- and NIH-funded research have given it strong relationships with endocrinologists on both sides of the Atlantic, and underpin its commercialization strategy.

"The plan for the company is to commercialize these products ourselves. It is a small space and we know a lot of the prescribers," Whitaker said.

Beyond Chronocort and Infacort the ambition is to become an endocrinology specialist targeting unmet needs in chronic hormonal diseases. "We have identified a number of such needs, which we estimate represent a combined market opportunity of more than $11 billion," said Whitaker.

Like its existing products, other replacement therapies will be based on established active pharmaceutical ingredients with no requirement for preclinical toxicology and a low relative risk, he said. //

IN THE CLINIC

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., said it filed a clinical trial application with the U.K. Medicines and Healthcare products Regulatory Agency for ALN-GO1, a subcutaneously administered investigational RNAi therapeutic for the treatment of primary hyperoxaluria type 1, a rare disease caused by failure to properly metabolize glyoxalate in the liver, Upon approval, the company plans to start a phase I study in early 2016 and expects to report initial data in late 2016.

Medigene

Continued from page 1

involving its spin-off company Catherex Inc., which Amgen is acquiring for $10.5 million up front plus regulatory and sales-based milestones, as well as single-digit royalty payments on Imlygic sales.

"The royalties are the more interesting part of the deal," Peter Llewellyn-Davies, chief financial officer at Martinsried, Germany-based Medigene, told *BioWorld Today*.

Further details of the deal have not been disclosed, but Catherex's position in using modified herpes simplex viruses (HSVs) in cancer therapy was obviously a strong one, if it was able to persuade Amgen to part with a share in the product's economics. The agreement, which runs until 2020, covers both the U.S., where Imlygic received FDA approval in October, and Europe, where Imlygic received formal approval from the European Commission in the past week.

Medigene originally gained ownership of the assets in question when it acquired San Diego-based Neurovir Therapeutics Inc., in a $77 million stock-based deal in 2001. It later spun out this business into Philadelphia-based Catherex Inc., while retaining a 40 percent equity stake. The remaining ownership rests with the team of scientific founders behind Neurovir, who include the high-profile virologist Bernard Roizman, of the University of Chicago. (See *BioWorld Today*, April 14, 2010.)

Catherex is an IP holding company only, as its active development programs – based on different underlying IP – were spun off last year into another entity, Aettis Inc., in which Medigene has a 39 percent stake.

Because of Imlygic's limited patent life – Llewellyn-Davies said it does not extend far beyond 2020 – Amgen aims to push its marketing efforts aggressively. Medigene will benefit from the resulting slipstream, as it seeks to make headway in the immuno-oncology field, where it has staked its future. Its 40 percent stake in Catherex converts into a 40 percent economic interest in the deal struck with Amgen.

Although Imlygic has modest activity – and modest commercial prospects – as monotherapy, it has real potential as combination therapy with agents such as immune checkpoint inhibitors, as it can boost their activity by establishing an inflammatory milieu within the tumor. Amgen, of Thousand Oaks, Calif., and Merck & Co. Inc., of Kenilworth, N.J., are planning a phase III combination trial of the agent and Merck's PD-1 inhibitor Keytruda (pembrolizumab), following promising interim phase Ib data from a melanoma trial, which they unveiled last month at the Society for Melanoma Research 2015 International Congress in San Francisco.

Medigene is in the process of completing its transition to a pure-play immuno-oncology company, which it began by acquiring Trianta Immunotherapies GmbH at the start of 2014. Trianta's scientific founder, Dolores Schendel, is about to move from her present position as Medigene's chief scientific officer to CEO of the company, succeeding Frank Mathias, who is joining its board. (See *BioWorld Today*, Jan. 28, 2014.)

As part of its strategic realignment, Medigene also disposed of its Endotag cancer program to Syncore Biotechnology Co. Ltd., of Taipei City, Taiwan, for €5 million (US$5.5 million), which is payable over five years.

Shares in Medigene (FRANKFURT:MEDI) gained more than 15 percent Monday, to close at €8.15. //

Brain

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synaptic connections is restored, which could have important implications for the management of neurological disorders such as epilepsy and possibly even autism, they reported in the Dec. 17, 2015, issue of *Cell Reports*.

Scientists from the RIKEN Brain Science Institute (BSI) and Nagoya University in Japan and the École Normale Supérieure in France demonstrated how inhibitory synapses were stabilized when the neurotransmitter, glutamate, signals the release of calcium ions from internal storage into the neuronal endoplasmic reticulum.

"Imbalances in excitation and inhibition in the brain have been linked to several disorders," said study lead author Hiroko Bannai, a designated lecturer in the Graduate School of Science at Nagoya University, explaining the significance of these new findings. "In particular, forms of epilepsy and even autism appear to be related to dysfunction in inhibitory connections."

"A dynamic balance between excitation and inhibition is crucial for brain functions such as the generation of rhythmic cortical network activities," said study co-lead author Fumihiro Niwa, a researcher in the Laboratory for Developmental Neurobiology at the RIKEN BSI.

"An excitatory/inhibitory balance is also important for the normal development of the brain," said Katsuhiko Mikoshiba, senior team leader in the Laboratory for Developmental Neurobiology at RIKEN BSI, noting that such an imbalance "may result in neurological disorders such as epilepsy or in neuropsychiatric diseases, including autism, schizophrenia and postpartum depression."

The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is one of the key regulatory molecules involved in maintaining the excitatory/inhibitory balance in the brain. When it binds to GABAA receptors on the neuronal surface, GABA prevents signaling to other neurons, with the strength of that inhibition depending on spacing of the surface receptors.

While GABAA receptors are normally clustered together, continual neural activation of N-methyl-D-aspartate (NMDA) receptors by another neurotransmitter, glutamate, as is seen naturally in epilepsy or during learning and memory, leads to excessive incoming calcium causing the receptors to become more widely dispersed, reducing neuronal inhibition by GABA. To counter that, the neuronal surface receptors are continually re-arranged, which maintains the proper excitatory/inhibitory balance in the brain.

In order to understand that better, the researchers focused on another signaling pathway that also begins with glutamate and is known to be important for brain development and control of neuronal growth. In that pathway, glutamate binds to the metabotropic glutamate receptor, mGluR, leading to the release of calcium into the neuron's internal environment.

Using an imaging technique called quantum dot-single particle tracking in cultured rat and mouse neurons, the team demonstrated that after release, this newly released calcium activated protein kinase C to promote clustering of GABAA receptors at the postsynaptic membrane, where the neuron receives incoming neurotransmitters from connecting neurons.

Those research findings established that glutamate activated distinct receptors and patterns of calcium signaling for opposing control of inhibitory GABA synapses.

"It was surprising that the same neurotransmitter that triggers GABAA receptor dispersion from the synapse, also plays a completely opposite role in stabilizing GABAA receptors, and that the processes use different calcium signaling pathways," said Nagoya University's Bannai. "This shows how complex our bodies are, achieving multiple functions by maximizing a limited number of biological molecules."

"The significance of this finding is that completely opposite actions at the same synapse resulting in dispersion vs. accumulation are mediated by the same signaling molecules, namely glutamate and calcium, but through an independent signaling pathway," commented Mikoshiba.

"Such a biological phenomenon has never been reported before," he noted, speculating "this may reflect the complexity of the human body realizing multiple functions, by maximizing limited species of biological molecules."

Pre-activation of the cluster-forming pathway completely prevented the dispersion of GABAA receptors that normally results from massive excitatory input, as seen in status epilepticus, in which a patient has consecutive epileptic seizures without recovery of consciousness.

"Further study of the molecular mechanisms underlying the process we have uncovered could help develop treatments or preventative medication for pathological excitation-inhibition imbalances in the brain," Niwa said.

"The most striking finding is that pre-activation of the mGluR/IICR/PKC pathway completely prevented the dispersion of synaptic GABAA receptors induced by massive excitatory input similar to status epilepticus," Mikoshiba told *BioWorld Today*.

"Thus, further study of the molecular mechanisms underlying the mGluR/IICR-dependent stabilization of GABAergic synapses via regulation of GABAA receptor lateral diffusion and inhibitory synaptic transmission could be helpful in the prevention or treatment of pathological excitation-inhibition imbalances, for example in the recovery of GABAergic synapses from epileptic states," he said.

"The next step in understanding how balance is maintained in the brain is to investigate what controls which pathway is activated by glutamate," said Bannai. "Most types of cells use calcium signals to achieve biological functions. On a more basic level, we believe that decoding these signals will help us to understand a fundamental biological question: Why and how are calcium signals involved in such a variety of biological phenomena?"

Mikoshiba said that other important questions that need to be

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Biosimilars

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cheaper biosimilars are too expensive for the general public. With numerous patient access challenges, biosimilars have had a difficult time finding their footing in some of these markets.

"All these projections of $20 billion, $10 billion, loss of exclusivity by 2020, prices going down 50 percent, it doesn't happen in reality," Sreedhar Sagi, head of medical affairs Asia-Pacific at Sandoz, a Novartis company, told *BioWorld Today*.

More developed markets, most notably New Zealand, have developed policies that ensure patient access, but not access to the market to biotech companies. New Zealand has a tender system in place, with a single drug in each category allowed for sale in the country that takes all pricing issues out of play while guaranteeing sales for the successful companies that get something of a monopoly for a time. Not every biosimilar maker can enter the market; they have to have regulatory approvals and established markets elsewhere. Because the government chooses one drug for the entire country, there are no marketing or significant sales costs.

"New Zealand has a very price-driven policy," said Sagi. "The money can be shifted to real need rather than buying biologics that are years old," Sagi said. "The doctors have only one choice of each biosimilar; it's one drug, one company and the doctor has to use it."

Sandoz is the generic pharmaceuticals division of Novartis and has marketed three biosimilars – a human growth hormone, G-CSF and epoetin alfa – that account for more than half of combined biosimilar sales in North America, Europe, Japan and Australia. It also has a pipeline of biosimilar molecules under development and registration including biosimilar rituximab and etanercept.

Like New Zealand, Malaysia also has a general tendering system but different policies. Because there are multiple players for a single product, companies have to fight for prescriptions. Adding sales and marketing costs results in higher prices.

Sagi said the New Zealand approach is a good one for countries with a relatively small population and high income. New biologics can cost patients tens of thousands of dollars per year, said Sagi.

BIOSIMILAR COPIES EMERGE

For countries where most of the people can't even afford biosimilars, a new type of product that Sagi calls "a third type of product" is emerging.

"There are copies of biosimilars manufactured in different countries in Asia and Latin American, which are far cheaper."

These products are not U.S. FDA- or EMA-approved "true biosimilars" but biologics that should have the same effect but are without clinical studies.

"The [World Health Organization] is even considering a third type of products that could be used in [low income] countries such as Laos, Cambodia, Vietnam, Chile and Peru, that don't have the economies or scales to afford the [U.S. and EU] approved biosimilars," he said.

The true biosimilars, even when they're already cheaper than originator drugs, still require plenty of clinical studies to prove biosimilarity. And that's adding up to the prices at the end.

"The clinical studies are where the cost goes up," he said. "For the third-wave products you need to show from an analytical point of view that they're the same molecules, probably PK [pharmacokinetic] or PD [pharmacodynamics] studies, then you get the license," he added. "If you can really prove your molecule is as close as the originator can be in each batch then there should be no problem."

AN EDUCATION CHALLENGE

Another factor that is blocking patients' access to biosimilars in Asia is the lack of a tracking system for postmarket studies and treatment outcomes, and a simple lack of trust among front-line physicians who are used to working with a particular drug.

"Regulators see the science and principles to approve product but physicians don't have the knowledge of manufacturing biosimilars and they have concerns of using these products because they can't track the drugs' safety, efficacy or side effects."

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Biosimilars

Continued from page 9

Sagi gave an example of a nephrologist in India that uses local copies made in India, Vietnam, Thailand or Argentina in his clinic.

An originator kidney drug could cost seven times more than local copies. And because of huge number of patients in India and lack of a tracking system, the doctors can't find out if the local copies work or not. There are also many rural patients who won't come back to the doctors again so they pretty much get whatever they can afford in one visit. Without this information, doctors often worry about the safety and efficacy of the cheaper biosimilars and hold back on prescribing these drugs.

Thailand has a better but similar situation where most of the patients won't revisit the doctor and tracking the patients' response to the drugs is very difficult.

"From an industry perspective, as long as you can prove [the similarity of] a true biosimilar, you can get the approval easily but that doesn't solve the problem because physicians don't want to use these products; they are not forced by the government to use biosimilars," said Sagi.

He said unless the government forces doctors to use the cheaper biologics (as in New Zealand), doctors can find excuses not to give them to patients. Physicians are used to a product and their patients are often stable with that choice and don't want to opt for a new biosimilar that requires monitoring from scratch.

PATIENT ACCESS PLAYS IN, TOO

And for the patients, since they are not paying any more or less due to either insurance or government programs the choice is meaningless. However, a cheaper version of a drug can help governments significantly lower health expenditures or cover more people with the same amount of money.

"It's not just the regulatory approval that makes sense; you need to push different factors for patient access," said Sagi.

In China, biosimilars have long been used in hospitals. Although they have to be approved as new drugs, they're still not the same as U.S.- or EU-approved biosimilars in terms of quality.

"The Chinese physicians' attitude toward biosimilars based on our research is that they believe if a drug is approved by the CFDA then they should use it," Helen Chen, director and partner of L.E.K. Consulting, told *BioWorld Today*. "They rely on the CFDA to tell them if it's safe."

The Chinese physicians do realize that these biosimilars are not fully interchangeable with the originators. The CFDA has released new regulations this year to further elaborate on the clinical studies requirement of biosimilar products. But the current marketed biosimilar products approved through the old approval system are not "true biosimilars" even though they have basic clinical facts. //

Brain

Continued from page 8

addressed in the future include how glutamate can selectively evoke calcium influx or release to achieve appropriate biological function, and by which parameters in calcium signaling the message is encoded.

"Most cell types utilize calcium signaling to achieve biological functions and we are currently developing better calcium imaging techniques, in order to achieve a more precise spatio-temporal resolution," he said

"We believe that decoding calcium signals will provide an insight into the fundamental problem of how and why calcium signaling can induce such a wide variety of biological phenomena. We also propose that the regulation of membrane molecular dynamics could represent the next generation of drug development strategies." //

Aveo

Continued from page 5

the firm is working to identify a "commercializable companion diagnostic" that could enable further development in that indication.

As of Sept. 30, Aveo had $37.2 million in cash, equivalents and marketable securities. It also has a couple of other assets it could seek to out-license, including AV-203, an ErbB3-inhibiting antibody partnered until 2014 with Biogen Inc. outside the U.S. AV-203 has completed a phase I study, showing no dose-limiting toxicity. //

OTHER NEWS TO NOTE

Emulate Inc., of Cambridge., Mass., announced an expanded research collaboration with **Merck & Co. Inc.**, of Kenilworth, N.J., to deploy Emulate's organ-chips across certain Merck discovery programs to improve models of human inflammatory diseases and to better predict the potential human response of therapeutic candidates. The research will focus on using Emulate's Small Airway Lung-Chip and Intestine-Chip to enable predictive modeling of inflammatory processes in the human lung and the gastrointestinal system. Emulate will retain rights to any resulting discoveries related to the Organ-Chip technology. In addition, Merck has the option to extend the collaboration to include additional organs, disease models or drug programs. Other terms of the agreement were not disclosed.

Faron Pharmaceuticals Ltd., of Turku, Finland, said the Finnish Funding Agency for Innovation (Tekes) has granted €1.535 million (US$1.675 million) in funding to progress the preclinical development of Clevegen, the firm's cancer immunotherapy drug candidate. The funding awarded is a government loan, which covers 50 percent of the budgeted cost of the preclinical development of Clevegen, which is designed to target Clever-1 cell surface receptors that are involved in cancer growth and spread.

OTHER NEWS TO NOTE

Foundation Medicine Inc., of Cambridge, Mass., said it inked a nationwide agreement with Unitedhealthcare for the use of Foundationone, Foundation's genomic profiling assay for solid tumors. Under the agreement, Unitedhealthcare covers Foundationone for those with metastatic stage IV non-small-cell lung cancer. The agreement became effective Dec. 15.

Genmab A/S, of Copenhagen, Denmark, achieved a $3 million milestone in its Duobody technology platform collaboration with Janssen Biotech Inc., a unit of New Brunswick, N.J.-based **Johnson & Johnson**. The milestone is triggered by Janssen's selection of a clinical candidate for the seventh program in the collaboration. Janssen has optioned 11 programs out of a total of 20 programs under the bispecific Duobody platform collaboration with Genmab. Including the collaboration with Janssen, Genmab has five commercial partnerships for its Duobody technology. Under the original July 2012 agreement, Janssen has the right to use the Duobody technology to create panels of bispecific antibodies to multiple disease target combinations. Genmab received an up-front payment of $3.5 million from Janssen and will potentially be entitled to milestone and license payments of up to about $175 million, as well as royalties for each commercialized Duobody product.

Janssen Pharmaceuticals Inc., of Raritan, N.J., part of Johnson & Johnson, said it established a collaborative and licensing agreement with **Bavarian Nordic A/S**, of Copenhagen, Denmark, which involves using Bavarian Nordic's MVA-BN technology along with Janssen's Advac technology to develop a heterologous prime-boost vaccine for human papillomavirus chronic infections that can lead to cancer. Under the terms, Janssen will conduct clinical development and, subject to regulatory approval, will be responsible for registration, distribution and commercialization of a combination vaccine worldwide. Financial terms were not disclosed.

Kiadis Pharma NV, of Amsterdam, announced a collaboration with the Thalassaemia International Federation to develop products to improve treatment of thalassemia patients and will be entering clinical development in the first quarter of 2016. Kiadis Pharma said its product, ATIR201, has the potential to address the current risks and limitations connected with hematopoietic stem cell transplantation (HSCT), being graft-vs.-host-disease, and make HSCT a first-choice treatment of beta-thalassemia major.

Lion Biotechnologies Inc., of New York, entered a collaboration to conduct clinical and preclinical research in immuno-oncology with Medimmune, a unit of **Astrazeneca plc**, of London. Lion will fund and conduct two phase IIa trials combining Medimmune's investigational PD-L1 inhibitor durvalumab with Lion's tumor-infiltrating lymphocytes (TIL) for the treatment of patients with metastatic melanoma, and head and neck cancer. Medimmune will supply durvalumab for the clinical trials. The purpose of the studies is to establish a dosing regimen for that combination therapy and assess its safety and efficacy. Preclinical research under the agreement will focus on identifying and evaluating therapeutically effective combinations of Medimmune's checkpoint antibodies, using TIL as an in vitro model of the tumor microenvironment. The research will be funded by Medimmune and conducted by Lion. Financial terms were not disclosed.

Medivir AB, of Huddinge, Sweden, said Janssen Pharmaceuticals Inc., a unit of **Johnson & Johnson**, of New Brunswick, N.J., terminated development of AL-704 (also known as JNJ-54257099) following completion of phase I studies conducted by Alios Biopharma Inc., a Janssen company. Those studies demonstrated that AL-704 was safe, well tolerated and had acceptable pharmacokinetic properties. However, its clinical antiviral activity in persons infected with hepatitis C virus (HCV) genotype 1 was insufficient to justify further clinical studies. No further compounds arising from Medivir's license agreement with Janssen on HCV NS5B polymerase inhibitors are expected to be progressed into clinical studies, and therefore no further revenues from the agreement will be received. Termination of the project does not affect the MIV-802 project, which is wholly owned by Medivir, nor any of the products or compounds in other partnerships with Janssen.

Neurelis Inc., of San Diego, received orphan drug designation from the FDA for the firm's lead program, NRL-1 (intranasal diazepam), for pediatric, adolescent and adult epilepsy patients who experience acute repetitive seizures. NRL-1 is a formulation of diazepam, delivered via an already-marketed nasal sprayer, being developed for the management of pediatric and adult patients who require intermittent use of diazepam to control bouts of acute repetitive seizure activity.

Novabay Pharmaceuticals Inc., of Emeryville, Calif., reported a 1-for-25 reverse stock split of all outstanding common shares Dec. 18. The effect will be to combine each 25 shares of outstanding company common stock into one new share, with no change in authorized shares or par value per share, and to reduce the number of common stock shares outstanding from about 87.1 million shares to about 3.5 million shares. The trading symbol, NBY, will not change.

Peptidream Inc., of Tokyo, reported a multitarget discovery and optimization collaboration with Genentech Inc., a unit of Basel, Switzerland-based **Roche AG**. Peptidream will use its Peptide Discovery Platform System (PDPS) technology to identify macrocyclic/constrained peptides against multiple targets of interest selected by Genentech, and will optimize hit peptides into therapeutic peptides or small-molecule products. Genentech will have the right to develop and commercialize all molecules resulting from the collaboration. Under the terms, Peptidream will receive an undisclosed up-front payment, research funding and is eligible for payments associated with the achievement of certain preclinical and clinical development milestones. In addition, Peptidream is eligible to receive royalties on sales of any products that arise from the collaboration. Roche retains an option to nonexclusively license the PDPS technology at a future date.

OTHER NEWS TO NOTE

Pharming Group NV, of Leiden, the Netherlands, and its partner, **Hyupjin Corp.**, of Seoul, South Korea, said Hyupjin received marketing authorization for Ruconest (recombinant human C1 inhibitor) in South Korea. Ruconest is approved for the treatment of acute angioedema attacks in adult patients with hereditary angioedema (HAE). Effectiveness was not established in HAE patients with laryngeal and oropharyngeal attacks. Ruconest is the only recombinant C1-INH approved by the FDA.

Samsung Biologics Co. Ltd., of Seoul, South Korea, broke ground on its third plant in Incheon Free Economic Zone, Songdo, Korea. Once it begins operation, Samsung Biologics said it would be the world's largest biologics contract manufacturing organization with a total production capacity of 360,000 liters.

Sernova Corp., of London, Ontario, said the European Commission's Horizon 2020 program has awarded a €5.6 million (US$6.1 million) grant to a Hemacure consortium involving the company and five European academic and private partners working on advancing development of a GMP clinical-grade factor VIII-releasing therapeutic cell product in combination with Sernova's Cell Pouch for the treatment of severe hemophilia A. The product being developed by the Hemacure consortium will seek to provide constant delivery of factor VIII to normalize blood levels.

IN THE CLINIC

Antibe Therapeutics Inc., of Toronto, said it completed validation studies initiated as a consequence of lead drug ATB-346 inducing an elevation of liver enzymes in some subjects taking the higher doses of the drug (750 mg/day and 1,500 mg/day). Results of the studies, aimed at gaining a better understanding of the drug's potency, absorption, metabolism and excretion characteristics, support progression to phase II development in patients with osteoarthritis, the company said. It plans to submit an application to Health Canada in early 2016.

Baxalta Inc., of Bannockburn, Ill., reported that Adynovate (antihemophilic factor [recombinant], pegylated) successfully met its primary endpoint in a phase III study designed to assess the safety and immunogenicity of the hemophilia A therapy, which gained FDA approval in November. The study enrolled 73 previously treated patients with severe hemophilia A younger than 12 years of age and assessed the treatment's hemostatic efficacy in prophylaxis and treatment of bleeding episodes. All participants received prophylactic Adynovate treatment (median 1.9 infusions per week) and were followed for six months. No patients developed inhibitory antibodies to Adynovate. In addition, no treatment-related serious adverse events were reported. With the study results, the company plans to file for marketing authorization in Europe and aims to file for a pediatric indication in the U.S. in early 2016. Adynovate is currently under regulatory review in Japan, Canada and Switzerland. Baxalta also reported that M923, a biosimilar version of Humira (adalimumab, Abbvie Inc.) that it is developing with Cambridge, Mass.-based **Momenta Pharmaceuticals Inc.**, met the primary endpoint of bioequivalence in a randomized, double-blind, three-arm, parallel group, single-dose study. The study, which included 324 healthy volunteers, compared M923 to both U.S.- and EU-sourced Humira. Safety and immunogenicity were also found to be comparable between the biosimilar and reference products. Baxalta and Momenta began a separate pivotal trial of M923 in chronic plaque psoriasis in October. The companies are targeting a first regulatory submission in 2017 and a first commercial launch as early as 2018. (See *BioWorld Today*, Nov. 17, 2015.)

Bionor Pharma ASA, of Oslo, Norway, reported that the combination of Vacc-4x, a vaccine comprising four engineered peptides that target conserved domains of the HIV p24 protein, and the latency-reversing agent Istodax (romidepsin, Celgene Corp.) led to control of reactivated HIV and reduction in latent viral reservoir during a phase Ib/IIa trial, confirming and extending the findings of an interim analysis announced in May. Data on viral load were obtained from 17 patients and 16 patients completed the trial. Once it has enough funding, Bionor expects to initiate a phase II, randomized, double-blind, placebo-controlled trial. The primary endpoint will be viral load during combination antiretroviral therapy after each of three romidepsin infusions in Vacc-4x-treated patients compared to placebo patients.

Celyad SA, of Mont-Saint-Guibert, Belgium, said the FDA authorized an investigational new drug application that will allow it to proceed with a phase III study of its lead cardiology candidate, C-Cure cardiopoietic cells delivered via the C-Cathez catheter, for heart failure in the Chart-2 trial in the U.S. The study, which is intended to assess the efficacy of C-Cure as a treatment for ischemic heart failure, is a randomized, double-blinded trial comparing treatment with C-Cure to a sham treatment. Celyad expects to recruit a minimum of 240 patients with chronic advanced symptomatic heart failure. (See *BioWorld Today*, Oct. 26, 2015.)

Excellthera Inc., of Montreal, said Health Canada approved the initiation of a phase I/II trial of its lead product, ECT-100, for the expansion of hematopoietic stem cells (HSCs). The trial, set to begin in early 2016, will enroll up to 25 patients who require stem cell transplantation for the treatment of acute myeloid leukemia and other malignant blood disorders, but who lack a suitable donor. ECT-100 is a combination of a small molecule, UM171, and bioreactor technology. ECT-100 expands blood progenitors (CD34+ cells) more than 100-fold and enables the significant expansion of primitive (undifferentiated) HSCs, which is anticipated to provide the robust long-term reconstitution of the blood-forming system from small samples of HSCs.

IN THE CLINIC

Histogenics Corp., of Waltham, Mass., said the FDA accepted an amendment to the Neocart phase III trial protocol to expand the eligible patient population. Changes are designed to help attract qualified candidates to the study. The company is on track to complete enrollment by the end of the second quarter of 2017. Among the changes: Patients with trochlear lesions will now be included in the trial; the upper age limit of patients eligible to participate in the trial will be increased from 55 years to 59 years; and the time between a prior procedure and a patient's participation in the study will be reduced. Also, patients with asymptomatic lesions in nonstudy locations that are larger than the study lesion will no longer be excluded from the trial. The trial is being conducted under a special protocol assessment.

Medivation Inc., of San Francisco, said it started a potential registrational phase II trial of MDV9300 (pidilizumab) in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The open-label study is expected to enroll about 180 patients with an incomplete response following salvage therapy or autologous stem cell transplantation for relapsed or refractory CD20+ DLBCL, transformed indolent lymphoma or primary mediastinal B-cell lymphoma. The primary endpoint of the trial is best overall response rate.

Merck & Co. Inc., of Kenilworth, N.J., announced results from the pivotal KEYNOTE-010 study, the first study of its kind to evaluate the potential of an immunotherapy compared to chemotherapy based on prospective measurement of PD-L1 expression in patients with advanced non-small-cell lung cancer. In the phase II/III study, Keytruda (pembrolizumab), Merck's anti-PD-1 therapy, significantly improved overall survival (OS) compared to chemotherapy in patients with any level of PD-L1 expression, as defined by a tumor proportion score (TPS) of 1 percent or more. Specifically, Keytruda resulted in a 29 percent improvement in OS for the 2-mg/kg dose and a 39 percent improvement in OS for the 10-mg/kg dose, compared to docetaxel. The estimated one-year OS rates for Keytruda were 43.2 percent and 52.3 percent, respectively, compared to 34.6 percent for docetaxel. The results were published in *The Lancet* and presented at the European Society for Medical Oncology Asia 2015 Congress. Merck plans to submit a supplemental biologics license application to the FDA by the end of 2015 and submit a marketing authorization application to the EMA in early 2016.

Mirati Therapeutics Inc., of San Diego, said it started a phase II study of glesatinib, the proposed generic name for MET/Axl inhibitor MGCD265, in non-small-cell lung cancer patients with activating genetic alterations of the MET gene, including MET gene amplification and MET mutations. The open-label, single-agent trial will enroll patients who have failed at least one prior treatment with platinum-based chemotherapy. The primary endpoint is objective response rate, and the secondary endpoint is progression-free survival.

Momenta Pharmaceuticals Inc., of Cambridge, Mass., said it resumed patient enrollment in its ongoing phase II portion of the phase I/II study testing M402 in combination with Abraxane (nab-paclitaxel, Celgene Corp.) and gemcitabine in patients with metastatic pancreatic cancer. Enrollment was paused last month following the company's acceptance of recommendations from its data monitoring board to develop guidelines for diagnosing and managing thrombocytopenia, based on a limited number of specific toxicities observed in the study. M402, or necuparanib, was engineered from unfractionated heparin to have significantly reduced anticoagulant activity while preserving antitumor properties associated with heparins. The drug previously received orphan drug and fast track designations in pancreatic cancer.

Pluristem Therapeutics Inc., of Haifa, Israel, reached an agreement with Japan's Pharmaceuticals and Medical Devices Agency (PMDA) on the design of the final trial needed to apply for conditional approval of PLX-PAD cells in the treatment of critical limb ischemia (CLI). The approval of the protocol for the 75-patient trial was part of a larger agreement on the development of PLX-PAD via Japan's new accelerated regulatory pathway for regenerative medicine. Patients will be randomized into three groups of 25. Group one will receive an initial 150 million PLX-PAD cell dose followed eight weeks later by a second 150 million cell dose; group two will be treated with an initial 300 million PLX-PAD cells followed eight weeks later by a second dose of 300 million cells; group three will receive two doses of placebo. The cells will be injected into a leg muscle using a standard syringe. Efficacy and safety will be determined from outcomes measured nine months after administration of the first dose. The primary efficacy endpoint will be diagnosis of a patient as CLI-free for 60 days. Pluristem expects to submit the formal clinical trial notification to the PMDA in early 2016.

IN THE CLINIC

Rxi Pharmaceuticals Corp., of Marlborough, Mass., said it initiated a phase II study, RXI-SCP-1502, testing the safety and clinical activity of Samcyprone, a topical formulation of diphenylcyclopropenone, on the clearance of cutaneous warts. The multidose trial will enroll subjects with at least one cutaneous, plantar or periungual wart present for at least four weeks. They will first be treated with a sensitization dose on the inner arm and on one preselected wart lesion, and once the sensitization response is confirmed, subjects will continue with weekly treatments for 10 weeks. Wart clearance will be evaluated based on Investigator's Global Assessment Score and wart measurements over time during the treatment period.

Sanbio Inc., of Mountain View, Calif., said it started patient recruitment for a phase IIb trial to further test the safety and efficacy of its cell therapy, SB623, for ischemic stroke. The ACTIsSIMA (Allogeneic Cell Therapy for Ischemic Stroke to Improve Motor Abilities) trial will examine SB623 cells, modified allogeneic mesenchymal stem cells, in patients who have experienced an ischemic stroke in the previous six months to five years and still suffer from motor impairments. About 156 patients are expected to be enrolled. The firm is working with **Sunovion Pharmaceuticals Inc.**, of Marlborough, Mass., a subsidiary of Sumitomo Dainippon Pharma Co. Ltd., under the terms of a development and license agreement for SB623 for chronic stroke in North America.

Sciclone Pharmaceuticals Inc., of Foster City, Calif., will pursue development and registration of SGX942 in the Greater China market, for the treatment of oral mucositis. SGX942 is being developed by **Soligenix Inc.**, of Princeton, N.J., which recently reported positive preliminary results from its phase II trial for the treatment of oral mucositis in head and neck cancer. SGX942 is an innate defense regulator, a new class of short, synthetic peptides designed to modulate the body's reaction to both injury and infection toward an anti-inflammatory and an anti-infective response. The phase II preliminary results reported by Soligenix showed a significant reduction in the duration of severe oral mucositis in patients receiving chemoradiation therapy for treatment of their head and neck cancers. In April 2013, Sciclone and Soligenix established a commercial collaboration in which Soligenix received access to Sciclone's oral mucositis clinical and regulatory data library in exchange for commercialization rights to SGX942 in the People's Republic of China, including Hong Kong and Macau. Specific terms were not disclosed.

Vernalis plc, of Winnersh, U.K., said it completed the CCP-07 pivotal single-dose comparative bioavailability study. CCP-07, the second product being developed for Vernalis by **Tris Pharma Inc.**, of Monmouth Junction, N.J., for the U.S. prescription cough-cold market, now will move into a multiple-dose comparative bioavailability study and continue 12-month stability studies. Subject to successful outcome of those trials, the filing of a new drug application remains on track for 2016. (See *BioWorld Today*, Feb. 13, 2012.)

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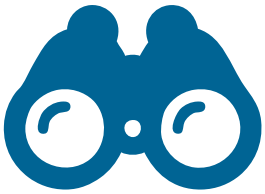

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