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CLEAN BRIEFING DOCS

Sneeze breeze? No FDA ragweed quibbles for Merck, Alk-Abello

By Randy Osborne, Staff Writer

Briefing papers for the meeting next week of the FDA's Allergenic Products Advisory Committee suggest that the panel will green-light the sublingual ragweed allergy therapy from Alk-Abello A/S and Merck and Co. Inc., just as the grass-pollen allergy tablet sailed through last month.

As with the grass-pollen allergy Grastek, the documents related to Ragwitek can't be used to predict what will happen at the meeting slated for Tuesday, but they contain no language that might indicate the FDA is skeptical about the safety or efficacy of

See Alk-Abello, page 3

Genmab raises $183M for pipeline, acquisitions

By Cormac Sheridan, Staff Writer

Taking advantage of a strong share price performance over the past 12 months, Genmab A/S added DKK998 million (US$183 million) to its coffers in an accelerated book-build involving selected institutional investors.

That takes its current cash position to about $450 million, giving it plenty of firepower to progress its internal pipeline

See Genmab, page 4

DEALS AND M&A

PARTNERING STRATEGIES

Australia's Hatchtech 'itching' to partner at J.P. Morgan

By Marie Powers, Staff Writer

As always, the 32nd Annual J.P. Morgan (JPM) Healthcare Conference offered an unparalleled partnering playground for pharmas and biotechs. Although the big

See Hatchtech, page 5

BENCH PRESS

BioWorld Science Editor Anette Breindl takes a closer look at **translational medicine**

Read this week's edition

See attachment

THE BIOWORLD BIOME

CHILDBIRTH: A BLOODY BUSINESS

Sex hormone controls blood stem cells

By Anette Breindl, Science Editor

Sex organs are controlled by sex hormones, to nobody's surprise – that's their point.

But now, researchers have shown that blood, too, is affected by sex hormones. Blood-forming stem cells in male and female mice differ in their abilities to divide and their response to estrogen, presumably to allow females to cope with the blood-forming demands of pregnancy and childbirth.

They published their findings in the Jan. 23, 2014, advance online issue of *Nature*.

As surprising as they are, the findings had to some degree been hiding in plain sight.

Senior author Sean Morrison told *BioWorld Today* that his team had noticed high variability in their studies of blood stem cells "for years . . . but no one

See Sex hormones, page 6

FINANCINGS

Beyond the 'Horizant': Xenoport adds $72M in upsized offering

By Jennifer Boggs, Managing Editor

On the heels of encouraging FDA feedback for a multiple sclerosis program and the possibility of profitability for marketed drug Horizant (gabapentin enacarbil) by the end of 2015, Xenoport Inc. is padding its coffers with a $72 million bumped-up public offering.

The Santa Clara, Calif.-based firm priced 12 million shares – originally it proposed to sell 10 million – at $6 apiece, marking only a slight discount to Thursday's closing price. Net proceeds will amount to about $67.3 million – $77.5 million if underwriters exercise their full allotment option.

Shares of Xenoport (NASDAQ:XNPT) closed Friday at $6.01, down 28 cents.

After a year in which the company dropped a late-stage program in spasticity on disappointing data and

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OTHER NEWS TO NOTE

Active Biotech AB, of Lund, Sweden, and **Teva Pharmaceutical Industries Ltd.**, of Jerusalem, said the European Committee for Medicinal Products for Human Use issued a negative opinion for Nerventra (laquinimod) for relapsing-remitting multiple sclerosis, concluding that the risk-benefit profile was not favorable at this time. The companies said they intend to request a re-examination of the opinion. Nerventra is a once-daily, oral central nervous system-active immunomodulator.

Aeolus Pharmaceuticals Inc., of Mission Viejo, Calif., received notice from the Office of Orphan Products Development at the FDA granting orphan status for AEOL 10150 for use in patients exposed to radiation following a nuclear accident or detonation in order to treat or mitigate acute radiation syndrome. Aeolus is developing AEOL 10150 as a treatment for the pulmonary and delayed effects of acute radiation exposure under a five-year contract with the Biomedical Advanced Research and Development Authority, a division of the U.S. Department of Health and Human Services.

Cardium Therapeutics Inc., of San Diego, began trading on the OTCQB Marketplace under the ticker symbol CRXM.

Cymabay Therapeutics Inc., of Newark, Calif., was cleared for quotation on the OTC Bulletin Board and the OTC Market Group's OTC Link quotation system under the ticker symbol CYMA.

Endocyte Inc., of West Lafayette Ind., provided an update regarding the review of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) on the pending European Union conditional marketing authorization applications for vintafolide, etarfolatide and intravenous folic acid. The CHMP has confirmed the questions it wants the firm to address, and an oral explanation by the company to the agency is expected to occur in the first quarter. If Endocyte is able to address the questions completely, an opinion from the CHMP could be rendered at the following monthly meeting.

Halozyme Therapeutics Inc., of San Diego, said the European Union's Committee for Medicinal Products for Human Use has recommended that the European Commission approve Basel, Switzerland-based **Roche AG**'s subcutaneous formulation of MabThera (rituximab) using partner Halozyme's recombinant human hyaluronidase (rHuPH20) for the treatment of patients with common forms of non-Hodgkin lymphoma.

Innovotech Inc., of Edmonton, Alberta, said its board approved a grant of stock options to management of Innovotech to purchase 50,000 common shares pursuant to its stock option plan. These options have an exercise price of about 4 cents per common share and expire on Jan. 22, 2024.

Pharmacell BV entered an agreement with **Tigenix NV**, of Leuven, Belgium, to purchase its cell therapy production facility at the Chemelot site in Sittard-Geleen, close to Maastricht, in the Netherlands, where Pharmacell is headquartered. Pharmacell will acquire the facility, including its team of employees, during the coming months. No terms were disclosed.

Protalix Biotherapeutics Inc., of Carmiel, Israel, said Health Canada completed a successful on-site evaluation of the company's manufacturing facility in Carmiel, as part of its ongoing review of the new drug submission for taliglucerase alfa in Gaucher disease. A decision on final marketing approval in Canada is expected this year.

STOCK MOVERS 1/24/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	-$89.47	-3.39%
Ariad Pharmaceuticals Inc.	+1.47	+19.55%
Biodelivery Sciences	+$3.16	+50.56%
Immune Pharmaceuticals	-$0.40	-14.88%

Biotechs showing significant stock changes Friday

BIOWORLD TODAY

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Alk-Abello

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Ragwitek. (See *BioWorld Today*, Dec. 13, 2013.)

The Ragwitek tablet contains an allergen extract from short ragweed pollen (Ambrosia artemisiifolia) sourced from the U.S., and would be dosed once daily in adults. Tested in five trials by Horsholm, Denmark-based Alk-Abello and Merck, of Whitehouse Station, N.J., Ragwitek underwent a 914-patient Phase III experiment, the largest of the studies.

Although adverse events did crop up in the trials, none "categorized as serious by investigators or the sponsor are considered related to the study drug," the FDA's briefing documents pointed out, and no patients died. The proposed treatment regimen with Ragwitek involves daily dosing for at least 12 weeks ahead of the onset of the allergy season and continuing through the end of it.

Ragweed grows in much of North America and, of all allergy sufferers in the U.S., 75 percent are allergic to ragweed, 50 percent to grasses and 10 percent to trees, according to the Medical University of South Carolina. Existing, somewhat primitive therapy consists mainly of immunotherapy – giving patients injections of tiny amounts of the allergen itself.

But synthetic vaccines are undergoing later-stage tests, too. Epalinges, Switzerland-based Anergis SA in October disclosed positive immunology results, after unveiling the first data during the previous month, from its Phase IIb trial with the treatment called Allert in the prevention of birch pollen allergy, showing significant clinical effects on multiple efficacy endpoints, including combined symptom and medication scores assessed daily throughout the natural birch pollen season of 2013. The company has a ragweed vaccine at the preclinical stage, as well as one for house dust mites. (See *BioWorld Today*, Oct. 21, 2013.)

Anergis is shopping for a partner to fund Phase III work. So is Circassia Ltd., of Oxford, UK, with its Toleromune technology, in which synthetic versions of epitopes identified from allergens are used to generate helper T cells. A Phase II trial in house dust mite allergy proved encouraging. Cat, grass and ragweed allergy products are in the works. (See *BioWorld Asia*, Sept. 18, 2013.)

Last October was hot for allergies. Bagneux, France-based DBV Technologies SA signed a licensing deal on a treatment for birch pollen allergy with major European player Stallergenes SA, of Antony, France, worth up to €145 million (then US$198 million) in milestone payments, with royalties if a marketed product results. (See *BioWorld Today*, Oct. 20, 2013.)

In the Ragwitek documents, the FDA noted that allergic rhinoconjunctivitis affects more than 500 million people globally, including about 30 million in the U.S. "While allergen avoidance and pharmacotherapy can provide significant relief, for many affected individuals symptoms remain," the FDA remarked. "For some of these patients, allergen immunotherapy is a reasonable alternative.

Subcutaneous allergen immunotherapy (SCIT) has been practiced since the early 20th century; the administration of allergen extracts orally or sublingually is a more recent development, increasing in Europe and the U.S.," the FDA wrote. "To date, U.S.-licensed allergen extracts for pollens, mold spores, animal danders, insects and inhalants are only approved for use in SCIT."

This seems about to change. Having a tablet such as Ragwitek would make treatment easier and patients more compliant, though the mouth also is the site where complications can arise for ragweed-allergy sufferers. Called oral allergy syndrome, it can arise when some patients eat any of ragweed's relatives, including fruits such as banana, cantaloupe, honeydew and watermelon, as well as vegetables such as cucumber and zucchini.

How well Ragwitek might work against oral allergy syndrome – with its itching, burning and swelling in the mouth and throat – remains an open question, as does market acceptance for both tablets given the advisory panel's blessing.

Another issue is whether patients will be as receptive as Alk-Abello/Merck hope, since those afflicted with allergies often are found to have multiple sensitivities, and the time-tested injections can be tailored to each person's needs. Analysts and allergy experts are projecting peak sales of Ragwitek that range from $300 million to $1 billion, depending the level of optimism about uptake.

Stallergenes also won the FDA panel's nod in December for a grass allergy tablet called Oralair, already well established in Europe.

Until now, the FDA had only approved subcutaneous therapies involving allergen extracts. Sublingual Oralair comprises extracts from Kentucky bluegrass, orchard grass, perennial rye grass, sweet vernal grass and Timothy grass. Alk-Abello/Merck's Grastek also is sold in Europe, under the brand name Grazax. (See *BioWorld Today*, Dec. 12, 2013.) //

OTHER NEWS TO NOTE

Provectus Biopharmaceuticals Inc., of Knoxville, Tenn., received the official minutes from the Type C meeting held with the FDA's Division of Oncology Products on Dec. 16, 2013. The purpose of the meeting was to determine which of the available paths that Provectus's oncology drug PV-10 will take in pursuit of initial FDA approval and commercialization. PV-10, a 10 percent solution of rose bengal disodium, is designed to selectively target and destroy cancer cells without harming surrounding healthy tissue, while inducing a secondary tumor-specific immune response. As a result of the meeting, Provectus will submit data from its Phase II study in a formal breakthrough therapy designation request this quarter, and should receive a decision within 60 days.

Genmab

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and to acquire or in-license additional products or technologies.

The offering comprised 4.6 million new shares, priced at DKK217 each, a slight discount on the company's closing share price of DKK228.50 on Thursday, immediately before it disclosed the transaction. The Copenhagen-based antibody developer exited the third quarter with DKK1.498 million in cash and forecast a year-end cash position between DKK 1,475 million and DKK1,525 million.

Thomas Bowers, analyst at Dankse Markets Equities, told *BioWorld Today* the financing was made possible by "the very positive environment for biotechnology right now – the money's there." Genmab's technology platform is "quite complete," he said, given its access to the Ultimab monoclonal antibody platform, its in-house-developed Duobody bispecific antibody platform and its Hexabody technology, which enhances antibody cytotoxicity.

Acquiring a linker technology could complete the jigsaw.

"That type of platform is something they are looking at," Bowers said, although he added that he does not expect any acquisition to happen in the near term. "It's not my impression they're involved in a late-stage process."

Genmab already has a partnership in this area with Bothell, Wash.-based Seattle Genetics Inc., from which HuMax-TF-ADC, an antibody-drug conjugate targeting tissue factor, has emerged. It entered Phase I trials in patients with locally advanced or metastatic solid tumors expressing tissue factor in December.

Genmab's stock has risen by about 100 percent over the past 12 months on the back of several deals with its Duobody technology and one mega deal, worth up to $1.1 billion, with its anti-CD38 antibody daratumumab, which the Janssen Biotech arm of Johnson & Johnson Co., of New Brunswick, N.J., has in-licensed. "It's a combination [of factors] but clearly daratumumab stands out, no doubt about that," Bowers said.

That drug, which is undergoing Phase II trials in multiple myeloma, is in direct competition with MOR202, another anti-CD38 antibody, which Martinsried, Germany-based Morphosys AG and Summit, N.J.-based Celgene Corp., are jointly developing. (See *BioWorld Today*, June 28, 2013.)

Genmab's sole approved product, Arzerra (ofatumumab), an anti-CD20 antibody marketed by its partner London-based Glaxosmithline plc, has struggled to make headway or gain mindshare against the might of the Roche blockbuster Rituxan (rituximab).

The drug, which is indicated for CLL that is refractory to fludarabine and alemtuzumab, took in $87 million in revenues for the first nine months of 2013 vs. the CHF5.2 billion (US$5.8 billion) that Rituxan, which is approved in multiple indications, clocked up during the same period.

"Right now it doesn't seem the market has much belief in the Arzerra program, compared with Gazyva [obinutuzumab] from Roche," Bowers said. The latter gained FDA approval on Nov. 1, 2013,and Basel, Switzerland-based Roche is positioning it as a successor to Rituxan, on the basis that it out-performed the latter in a head-to-head trial in CLL. (See *BioWorld Today*, July 25, 2013, and Nov. 2, 2013.)

Arzerra has an April 19 PDUFA date on an extension into first-line CLL therapy, but in the absence of head-to-head data against Rituxan, it remains difficult to see how it can make much headway in this indication. Head-to-head trials against Rituxan are under way in patients with relapsing or persistent CD20-positive diffuse large B-cell lymphoma who have already completed Rituxan therapy, and in patients with follicular lymphoma who have relapsed after Rituxan. It is also being studies in Waldenström's Macroglobulinemia, a type of slow-growing non-Hodgkin's lymphoma, in multiple sclerosis and in pemphigus vulgaris, an autoimmune disorder of the skin.

The new shares comprise about 8.9 percent of the company's pre-money share base. After the transaction, it will have 56,355,722 shares outstanding. The company's stock (COPENHAGEN:GEN) dropped almost 4 percent to close at DKK220 Friday, valuing the company at DKK11.38 billion. "We have a 'buy' recommendation on the stock," Bowers said.

Genmab officials were unavailable for comment because of U.S. legal restrictions. //

OTHER NEWS TO NOTE

PTC Therapeutics Inc., of South Plainfield, N.J., said the European Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion on the marketing authorization application for conditional approval of ataluren for the treatment of nonsense mutation Duchenne's muscular dystrophy. That response is consistent with the company's previous guidance concerning the substantial risks regarding conditional European Medicines Agency approval. PTC is conducting a 48-week, 220-patient confirmatory Phase III trial, which is on track to complete enrollment in the middle of this year, with top-line data expected in mid-2015. PTC said it intends to request a re-examination of the CHMP opinion with a final outcome expected in the second quarter of 2014, when the confirmatory study is expected to be more fully enrolled.

Seattle Biomedical Research Institute, a nonprofit research center based in Seattle, said researchers identified two HIV-1 envelope immunogens that elicit broadly neutralizing antibodies when introduced as a vaccine. The immunogens elicited cross-reactive binding antibodies to the variable regions 1 and 2 region of the envelope protein and induced antibodies capable of neutralizing an array of HIV from different subtypes. Data were published in *PLOS One*.

Hatchtech

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players generated most of the headlines, hundreds of smaller companies looked to JPM as the setting where they might punch their ticket to success.

Australia's Hatchtech Pty. Ltd. was one of those hopefuls, seeking the end game for a technology the company has pursued for nearly a decade. Its next-generation head lice treatment, Deovo, is poised to enter a pivotal Phase III study next month. If all goes well, the product could launch next year. JPM provided the opportune venue to pursue a partner for the company's only asset.

Hatchtech didn't actually get an invite to JPM, but that didn't prevent CEO Hugh Alsop from making the trip to San Francisco from the company's headquarters in Victoria. Alsop joined the specialty pharma in March 2013 from Phosphagenics Ltd., of Melbourne, where he served as vice president of operations and business development, overseeing the company's opioid transdermal patch development programs.

Prior to that, Alsop was director of business development at Australia's Acrux Ltd., where he played a key role in the company's licensing of testosterone solution Axiron to Eli Lilly and Co. in March 2010. At the time, the potential $335 million deal, including $50 million up front, was the largest single-product licensing deal by an Australian biotech. (See *BioWorld Today*, March 17, 2010.)

Alsop was drawn to Hatchtech – which simultaneously revamped its board of directors, adding former Acrux CEO Richard Treagus – with the singular goal of moving the company's only product out the door and into the arms of a commercial suitor.

"I've been through this process before," Alsop told *BioWorld Today* in San Francisco.

Alsop was a presenter at Biotech Showcase 2014, held in conjunction with JPM, which gave Hatchtech visibility in an increasingly large forum. But the main thrust of his trip was to set the wheels in motion for a transaction around Deovo once Phase III data report.

The topical lotion contains an inhibitor of metalloproteinases, which are critical to survival at all stages of the louse life cycle, from egg to adult. The company completed a Phase II safety and pharmacokinetics study of the gel that enrolled 38 children and adolescents before conducting a randomized, double-blind Phase IIb efficacy and safety study that enrolled 142 children at two U.S. sites, testing two doses of a single application of the gel against placebo.

The IIb primary efficacy results were statistically significant and clinically relevant in both treatment groups compared to control, with nearly 9 in 10 patients in the higher dose group lice-free 14 days after a single 10-minute treatment compared to fewer than 4 in 10 in the placebo group. Safety also was demonstrated, with no serious adverse events reported.

Based on the findings, Hatchtech met with the FDA last year to discuss a Phase III program, which was granted a special protocol assessment by the agency.

The Phase III trial, expected to begin the first week of February, will enroll upward of 600 patients at 14 U.S. sites. Since each patient will receive a single treatment and 14-day follow-up, the study should progress quickly, Alsop said. He expects Hatchtech to report data in the third quarter and to file a new drug application (NDA) with the FDA by year-end.

Once Phase III results are in hand, Hatchtech will seek an outright sale or structured transaction for the product, depending on which offers greater value to the company. Hatchtech has 23 shareholders – among them, the University of Melbourne, where the technology was first developed, and a number of high net worth individuals – so there's "pressure for an exit," Alsop acknowledged.

That said, "We have a fully differentiated product," he noted, with Deovo – which has broad patent protection in the world's major markets – representing the first innovation in decades to treat head lice.

"It is a niche opportunity, but being a late stage, fully funded program" with an NDA filing in sight, Deovo attracted significant interest in San Francisco, according to Alsop. Hatchtech is pursuing potential partners with established marketing and sales outreach to pediatricians, who represent target prescribers.

"We're getting the meetings," Alsop said.

In October 2013, Hatchtech raised A$12.6 (US$11.1), enabling the company to complete the Phase III and have breathing room to negotiate. The funding also was sufficient for Hatchtech to engage in early commercialization efforts, including the establishment of a contract manufacturing organization and production of registration batches for product launch. In addition, Hatchtech is starting to conduct market research on payers to determine an appropriate price point for Deovo as a prescription drug in the U.S.

Deovo also is attracting interest in Europe and Asia, including from potential partners with a global marketing presence, but "it will take some time to get data" from the U.S. that will help to penetrate other markets, Alsop said.

Alsop didn't necessarily identify new prospects in San Francisco. "We know who they are," he said.

Nevertheless, JPM provided an invaluable setting to promote the commercial potential of Deovo in one fell swoop to everyone who's anyone in the biopharma world.

"We're based in Australia," Alsop observed. "We have to find creative ways to partner." //

Sex hormones

Continued from page 1

had picked up on the fact that the variability correlated with the sex of the mouse.

"It's kind of remarkable," he added, "that no one has seen this before."

Morrison, who is at the University of Texas Southwestern Medical School's Children's Medical Research Center, and his team looked at the effects of estrogen on blood stem cells as part of a larger effort to look at systemwide regulation of stem cells.

Part of the reason no one had noticed estrogen's effects on blood stem cells, he contended, is that "there's been a tendency in stem cell biology to focus on local regulation."

But he argued that it's important for the local authorities to know what the rest of the organism is doing.

"If, for example, your body is starving, all of your tissues need to know that, so that they don't embark on major remodeling of a tissue or organ while you don't have the energy for it."

Likewise, in women, "all of your tissues need to know you're pregnant – it's a whole-body experience."

In their experiments, Morrison and his colleagues showed that both male and female blood stem cells express estrogen receptors, and that treating males as well as females with estrogen stimulated the stem cells to divide more frequently and produce more red blood cells. Genetically deleting the estrogen receptor from blood stem cells left them insensitive to estrogen, showing that the effect was a direct one.

Morrison stressed that neither his team nor anyone else has demonstrated estrogen's effects on blood-forming stem cells in humans, and that such an effect would be hard to test directly, because the most direct way of seeing an effect would involve repeated biopsies of the bone marrow.

But if the same effects do occur in humans, the findings "could have pretty broad implications, at least for young women that still have high estrogen levels."

He noted that the toxicity of chemotherapy and radiation damage dividing cells, and blood stem cells are one major category of cells affected by such treatments.

It might be useful to either take estrogen levels – which fluctuate with the menstrual cycle and are four times as high shortly before as after ovulation – into account, or to treat women with an estrogen inhibitor before chemotherapy to minimize stem cell activity during treatment. Conversely, estrogen might be used to stimulate the production of red blood cells.

The findings open up the possibility that some blood cancers are fueled by estrogen in the same way that many breast cancers are – a possibility that, if it turns out to be true, would suggest that such cancers might benefit from the same estrogen blockers that are used to treat those breast cancers.

"There's a lot of things we'd like to test now," Morrison said. For the time being, those tests will be in mice. But ultimately, he said, "there are numerous clinical opportunities to pursue." //

OTHER NEWS TO NOTE

Shire plc, of Dublin, on Friday completed a tender offer for all of the outstanding shares of **Viropharma Inc.**, of Exton, Pa. As of midnight on Jan. 23, 2014, approximately 53,745,956 common shares of Viropharma (excluding 3,597,087 common shares of Viropharma guaranteed to be delivered within the next three Nasdaq trading days) had been validly tendered and not withdrawn pursuant to the tender offer, representing approximately 79.5 percent of the outstanding common shares of Viropharma. Shire or certain of their respective subsidiaries or holders who have properly demanded appraisal rights under Delaware law) will be converted into the right to receive $50 per share in cash, the same price that was paid in the tender offer. Following completion of the merger, Viropharma will become a wholly owned subsidiary of Shire and its shares will cease to be traded on Nasdaq. The buy gives Shire a tight grip on the market for hereditary angioedema treatments, with the leading products for prophylaxis and for treating acute attacks both residing in the same portfolio. (See *BioWorld Today*, Nov. 12, 2013.)

FINANCINGS ROUNDUP

Cynapsus Therapeutics Inc., of Toronto, said 125,324 warrants with an exercise price of $0.575 have been exercised for total proceeds of $72,062. The company now has 39,009,335 common shares, 21,426,439 warrants and 2,691,316 options to purchase common shares outstanding.

Emergent Biosolutions Inc., of Rockville, Md., said it priced its offering of $215 million aggregate principal amount of convertible senior notes due 2021 in a private placement to qualified institutional buyers. The size of the offering was upsized from their previously announced $200 million. The company also granted the initial purchasers an option to buy up to an additional $35 million of the notes. Emergent intends to use majority of the net proceeds from the offering to finance their acquisition of **Cangene Corp.**, of Winnipeg, Manitoba, disclosed late last year. (See *BioWorld Today*, Dec. 13, 2013.)

Ophthotech Corp., of New York, said it received payment of approximately $41.7 million in a second tranche in royalty financing from **Novo A/S**. The payment was triggered as a result of the company reaching an initial enrollment milestone of a specified number of patients in its pivotal, multinational Phase III program of Fovista, an anti-platelet-derived growth factor (PDGF) compound that is being studied in combination with anti-vascular endothelial growth factor (VEGF) therapy for the treatment of neovascular age-related macular degeneration (wet AMD). Patient enrollment in the trial began in August 2013, and initial top-line data is expected in 2016. The company signed a $125 million royalty agreement with Novo A/S in May last year and received initial funding at that time. The third potential funding is based upon a further patient enrollment milestone. (See *BioWorld Today*, May 29, 2013.)

Xenoport

Continued from page 1

regained sole commercial responsibility for Horizant upon termination of its troubled partnership with London-based Glaxosmithkline plc, Xenoport looks to get back on track in 2014. (See *BioWorld Today*, May 21, 2013.)

For starters, the company reported "substantial progress" in sales of Horizant, approved in postherpetic neuralgia and restless legs syndrome in a business update earlier this month. CEO Ronald W. Barrett predicted that the "Horizant business will reach break-even and turn profitable by the end of 2015."

A weak start to sales following initial approval in 2011 prompted Xenoport to file suit against GSK and resulted in the companies ending their agreement in the first half of 2013. (See *BioWorld Today*, Nov. 12, 2012.)

Xenoport now retains worldwide rights to Horizant, except for Japan and other Asian territories, where the drug is sold by Astellas Pharma Inc.

But much of Wall Street's excitement on Xenoport these days is centered on its XP23829 candidate, a fumaric acid ester prodrug. It's similar to Biogen Idec Inc.'s Tecfidera (dimethyl fumarate), which has emerged as the standout multiple sclerosis (MS) therapy since its approval less than a year ago. (See *BioWorld Today*, March 29, 2013.)

Xenoport hopes to make use of the existing data for Tecfidera in developing its drug in relapsing forms of MS. In its business update, the firm said it believes, based on the recent feedback from the FDA's Division of Neurology Products, the agency might allow it to move straight into Phase III development in MS with doses of XP23829 that produce monomethyl fumarate (MMF) exposure similar to Tecfidera's.

At the same time, the FDA recommended that Xenoport explore other dosages of XP23829.

Wells Fargo analyst Brian Abrahams wrote in a Jan. 13 note that Phase III studies in MS could begin in 2016, with a potential MS approval in 2021. And, even though current plans call for the typical two-trial Phase III program, "one cannot rule out the possibility FDA might lessen the typical requirements if warranted by safety and MMF [pharmacokinetics/pharmacodynamics]."

If it reaches market, Abrahams added, XP23829 could have "tolerability advantages" over Tecfidera, "enabling it to take some share of the oral MS opportunity."

Development of XP23829 could be hastened if the agency allows Xenoport to file under the 505(b)(2) pathway, and the company said the FDA has required additional information before making a determination. Both the company and analysts, however, seem to think it unlikely.

Besides pursuing a 505(b)(2) approach would have required Xenoport to wait for certain Biogen patents "to run out and engage in a patent battle, which could have taken time," erasing any timetable advantages gained by waiving some Phase III trial demands, Abrahams noted. "While this may disappoint some who were hoping [Xenoport] could take this development 'shortcut,' we are not surprised and believe [Xenoport] adequately prepared the Street that a 505(b)(2) was not their preferred path anyway."

Plans for XP23829 also include development in psoriasis, and Xenoport anticipates filing an investigational new drug application later this year for a Phase II study in patients with moderate to severe plaque psoriasis.

Though partnership discussions are ongoing, Abrahams said he doesn't see Xenoport ceding control of XP23829 any time soon. "Our sense was that the company's preference would be to maintain control of the asset for as long as possible to try and optimize its value, potentially partnering following psoriasis data readout."

Given those considerations, the recent financing was hardly a surprise. Proceeds from the public offering, which will add to the $74.3 million in cash as of Sept. 30, 2013, will be used for working capital and general corporate purposes, including R&D expenses, selling, general and administrative expenses and manufacturing.

Credit Suisse Securities LLC is acting as sole book-running manager, while RBC Capital Markets LLC and Wells Fargo Securities LLC are serving as co-managers.

The offering is set to close on or about Jan. 29, after which Xenoport will have about 59.7 million shares – 61.5 million if overallotments are exercised in full – outstanding. //

FINANCINGS ROUNDUP

Tonix Pharmaceuticals Holding Corp., of New York, said it priced an underwritten public offering of 2,898,550 shares of its common stock at $15 per share. The company has also granted to the underwriters a 45-day option to acquire an additional 434,782 shares to cover overallotments in connection with the offering. After the underwriting discount and estimated offering expenses, the company expects to receive net proceeds of approximately $40.7 million, assuming no exercise of the overallotment option. The company said it plans to use the net proceeds to support the continued development of TNX-102 SL for the treatment of fibromyalgia, to initiate clinical trials of TNX-102 SL for the treatment of post-traumatic stress disorder and to initiate clinical trials of TNX-201 for tension-type headache. In December, they began enrolling subjects in an open-label extension study following the BESTFIT trial of TNX-102 2.8-mg sublingual tablet in fibromyalgia. The primary objectives are long-term safety and tolerability. The secondary objective is long-term efficacy for the symptoms of fibromyalgia. (See *BioWorld Today*, Dec. 11, 2013.)

CLINIC ROUNDUP

Endo Pharmaceuticals Inc., of Malvern, Pa., a subsidiary of Endo Health Solutions Inc., and **Biodelivery Sciences International Inc.**, of Raleigh, N.C., reported positive top-line results from the pivotal Phase III study of BEMA buprenorphine in opioid-naive subjects. The enriched-enrollment, double-blind, randomized withdrawal study met its primary efficacy endpoint, showing that BEMA buprenorphine resulted in improved chronic pain relief ($p < 0.005$) compared to placebo. Secondary endpoints supported of the efficacy of BEMA buprenorphine compared to placebo. The most commonly reported adverse events associated with buprenorphine compared to placebo were nausea (10 percent vs. 8 percent), vomiting (4 percent vs. 2 percent) and constipation (4 percent vs. 2 percent). Locking of the database for the opioid-naive study triggered a $10 million milestone payment from Endo to Biodelivery, based on a licensing agreement inked in January 2012. BEMA buprenorphine is in development to treat moderate to severe chronic pain around the clock for an extended period of time both in patients who are opioid-naive and opioid-experienced. A second Phase III study of BEMA buprenorphine in an opioid-experienced patient group is ongoing, with data expected to report in the second half of 2014. On Friday, shares of Biodelivery (NASDAQ:BDSI) shot up 50.6 percent, or $3.16, to close at $9.41, while Endo (NASDAQ:ENDP) lost 60 cents, closing at $65.75.

E-Therapeutics plc, of Oxford, UK, said patient recruitment into Phase I trials of ETS2101 in brain cancer and in solid tumors was halted temporarily due to a drug supply issue. Patients already receiving ETS2101 are continuing to be dosed in accordance with trial protocols, and the company plans to resume recruitment as quickly as possible. However, reporting of top-line data from the solid tumor study under way at three UK centers may be delayed beyond the end of the first quarter.

Infinity Pharmaceuticals Inc., of Cambridge, Mass., said preliminary data from an ongoing Phase I study showed that IPI-145, its lead oral inhibitor of phosphoinositide-3-kinase (PI3K)-delta and PI3K-gamma, was clinically active in relapsed/refractory T-cell lymphoma. Among 26 patients evaluable for response, the overall response rate was 38 percent, including one complete response and nine partial responses. The company said IPI-145 was generally well tolerated, with the most common Grade 3 side effects including increases in the liver enzymes ALT or AST, rash or fatigue. Data also suggested that treatment with IPI-145 led to decreases in serum levels of cytokines and chemokines known to play roles in lymphocyte trafficking and function, supporting the rationale that inhibiting PI3K-delta and PI3K-gamma offers the potential for therapeutic benefit in T-cell lymphoma and other blood cancers. The findings were reported during a poster presentation at the Annual T-Cell Lymphoma Forum in San Francisco. On Friday, the company's shares (NASDAQ:INFI) lost 82 cents, closing at $13.37. (See *BioWorld Today*, Sept. 26, 2013.)

Novocure, of Haifa, Israel, said the first patient was enrolled in the open-label, pilot EF-20 Study, designed to examine NovoTTF therapy plus gemcitabine as first-line therapy in locally advanced and metastatic pancreatic adenocarcinoma. NovoTTF therapy is an anti-mitotic treatment delivered continuously with a wearable, home-use medical device. The EF-20 Study plans to recruit 20 patients from centers in Spain, Germany and Switzerland.

PHARMA: OTHER NEWS TO NOTE

Dainippon Sumitomo Pharma Co. Ltd., of Osaka, Japan, and **Takeda Pharmaceutical Co. Ltd.**, also of Osaka, said the Committee for Medicinal Products for Human Use of the European Medicines Agency issued a positive opinion for lurasidone for the treatment of schizophrenia in adults. Lurasidone is a once-daily oral treatment that is currently available in Switzerland, the U.S. and Canada.

Valeant Pharmaceuticals International Inc., of Laval, Quebec, completed the previously announced transaction in which a wholly owned subsidiary of Valeant Pharmaceuticals International would acquire Solta Medical Inc. at a price of $2.92 per share in cash, or approximately $250 million in the aggregate.

BENCH PRESS

BioWorld looks at translational medicine

By Anette Breindl, Science Editor

PARP-1: BRCA to coca?

To biopharma folks, poly(ADP-ribose) polymerase-1 (PARP-1) is best known as a synthetic lethal gene in BRCA-mutated cells. But scientists at the Mount Sinai School of Medicine have shown that PARP-1 plays a role in a very different disease, namely addiction. In its studies, the group looked at PARP-1 in the brain's reward center and found that its expression was increased in response to chronic cocaine treatment. That increase led to altered behavioral responses to cocaine, including increased self-administration, in the animals. Molecularly, the increases caused higher levels of another protein, side-kick 1. The authors said their findings "implicate PARP-1 and its numerous target genes as potential sites of pharmacological intervention in the treatment of cocaine addiction." They published their experiments in the Jan. 21, 2014, issue of the *Proceedings of the National Academy of Sciences*.

How the liver gets its blood

Scientists from the German Cancer Research Center have gained new insights into the role that endothelial cells play in controlling liver regeneration. Endothelial cells line blood vessels, and it is becoming increasingly clear that they are organ-specific and influence the organs they find themselves in. (See *BioWorld Today*, Nov. 11, 2010.) One of the newly recognized roles of endothelial cells is that they promote regeneration after injury. In their work, the authors showed that after liver injury, the precise timing of liver cell regeneration followed by blood vessel regeneration was controlled by the level of the growth factor angiopoietin-2, which was secreted by endothelial cells. At first, low levels of angiopoietin-2 enabled liver cells to grow, while later, higher levels of the protein, and its receptor, led to increased blood vessel formation to supply the newly made liver tissue with oxygen and nutrients. The authors published their work in the Jan. 24, 2014, issue of *Science*.

Bring in the anti-tank machinery

Scientists from the Chinese Beijing Institute of Biotechnology have identified the TANK-binding kinase 1 as a kinase that predicts tamoxifen resistance in breast cancer and so could be both a biomarker and a therapeutic target. The majority of breast cancers are fueled by estrogen, and resistance to anti-estrogen therapies such as tamoxifen is a major clinical problem in their treatment. In their experiments, the team discovered that TANK-binding kinase 1, which plays a role in the innate immune system, also phosphorylated the estrogen receptor, which increased the transcription of the receptor. In cell culture, forced expression of TANK-binding kinase 1 decreased their responsiveness to tamoxifen, and in tumor samples from breast cancer patients, high levels of TANK-binding kinase 1 correlated with high levels of estrogen receptor and poor response to tamoxifen. The authors concluded that TANK-binding kinase 1 "is potentially a unique predictive marker of tamoxifen resistance and a potential therapeutic target for breast cancer." Their findings appeared in the Jan. 21, 2014, issue of the *Proceedings of the National Academy of Sciences*.

Estrogen and epilepsy

Estrogen may fuel many breast cancers, but another study, from researchers at Baylor College of Medicine, suggested it may be useful for treating some severe seizures. In their work, the authors looked at the effects of estradiol, which is a form of estrogen, on an X-linked severe seizure disorder called infantile spasms syndrome, which leads to mental retardation and severe muscle spasms in adulthood. They found that treating mice with the disorder early on, before the onset of puberty, prevented seizures in the infant mice and spasms in adults. Treatment in adults was ineffective. Estradiol worked by restoring the numbers of inhibitory interneurons that are depleted in infantile spasms syndrome, and the authors suggested that "postnatal [estradiol] treatment may induce lasting transcriptional changes that lead to enduring disease modification and could potentially serve as a therapy for inherited interneuronopathies." Their work appeared in the Jan. 24, 2014, issue of *Science Translational Medicine*.

From acid to excitement

Scientists from the Japanese Tohoku University Graduate School of Medicine have shown that glial support cells in the brain contribute to toxicity and neuronal cell death during a stroke. During a stroke, the two most striking changes to the cellular environment are that it becomes more acidic, and that it comes to contain very high levels of glutamate, which kills neurons through excessive activation. Why cells release so much glutamate had not been worked out, and the authors showed that this release is connected to the increased acidity of the extracellular environment, which was due to the activation of a cation channel on glial cells. The authors said their results showed "a causal relationship between glial acidosis and neuronal excitotoxicity," and that "controlling glial pH may be an effective therapeutic strategy for intervention of ischemic brain damage." Their findings were published in the Jan. 22, 2014, issue of *Neuron*.

BENCH PRESS

Continued from previous page

Mom's insulin alters baby's brain

Researchers from Yale University and the German Max-Planck-Institute for Neurology have shown that deregulated insulin signaling during pregnancy partially underlies so-called metabolic programming, in which a mother's diet during pregnancy programs her offspring's metabolism – unfortunately, most often for the worse. Epidemiological and other research has shown that both being overweight and eating a high-fat diet during pregnancy predisposes a woman's offspring for metabolic problems. In animal studies, the scientists showed that what they termed "maternal overnutrition" during suckling – a period that corresponds to the third trimester of pregnancy in humans – altered the development of neuronal circuits in parts of the brain that are involved in feeding, and that such alterations could be partially prevented through making those circuits insensitive to insulin. The authors concluded that "our results point toward the necessity of highly sensitive glucose tolerance screenings and well-controlled antidiabetic therapy for mothers – particularly during this distinct phase of pregnancy – independent of their body mass index." Their findings appeared in the Jan. 24, 2014, issue of *Cell*.

Monocyte targeting decreases inflammation

Scientists from Northwestern University and the Australian University of Sydney have developed a particle that specifically targeted monocytes for destruction. Monocytes are a type of immune cell that contributes to many inflammatory disorders, but to date, no specific targeting strategies existed for that cell type. The authors developed what they termed immune modifying nanoparticles that specifically targeted monocytes. Cells that took up the particles no longer homed to sites of inflammation; instead, they were sequestered in the spleen. The authors tested their particles in several disease models, including cardiovascular disease and multiple sclerosis. They found that treatment with the particles reduced disease symptoms and promoted tissue repair. Cour Pharmaceutical Development Co. Inc., which had co-authors on the paper, hopes to develop the particles for the treatment of heart disease and other indications. The study appeared in the Jan. 16, 2014, issue of *Science Translational Medicine*.

Don't take your vitamins?

Scientists from the Canadian University of Toronto have discovered that "Folic Acid Supplementation Promotes Mammary Tumor Progression in a Rat Model," which is the title of the paper they published describing their results. Much of the population of North America, including many cancer survivors, takes multivitamin supplements in the expectation that they will confer health benefits. But the actual effects of those supplements are complex and often controversial. Animal studies have shown that folic acid may prevent the development of cancer in the first place, yet also promote the progression of tumors once they are established. In their work, the authors showed that if rats had pre-existing breast tumors, folic acid supplementation caused those tumors to grow more quickly. Folic acid intake has increased over the past few decades, and the authors cautioned that "the potential tumor-promoting effect of folic acid supplementation in breast cancer patients and survivors needs further clarification." The work appeared in the Jan. 21, 2014, issue of *PLoS ONE*.

What cytokine storms are good for

Scientists from the Canadian Children's Hospital of Eastern Ontario Research Institute have found that combining SMAC mimetics and innate immune stimuli synergized to kill cancer cells. SMAC is a pro-apoptotic protein that, when it is released from mitochondria, binds to anti-apoptotic proteins and induces cell death. Several rationally designed SMAC mimetic compounds are in clinical trials for treating cancer, but so far, their safety has been better than their efficacy – they appear to work only in tumor types that naturally produce large quantities of pro-apoptotic signals. One class of such signals is the proinflammatory cytokines, and the authors reasoned that inducing a safe level of cytokine storm might synergize with the effects of SMAC mimetic compounds. They found they were able to do so through the use of oncolytic viruses and vaccine adjuvants, prompting them to argue that "it may be worthwhile to explore their clinical efficacy in combination with [SMAC compounds mimetics]." They published their experiments in the Jan. 26, 2014, advance online issue of *Nature Biotechnology*.

Drug-resistant TB: worst of both worlds

Researchers from the British Queen Mary University London have reported results from a large-scale sequencing study of Russian tuberculosis isolates. Tuberculosis infects about a third of the world's population, and among infectious diseases is second only to HIV in the number of deaths it causes. Drug resistance – both multidrug resistance (MDR) and the even more serious extensive drug resistance (XDR) – are becoming serious concerns, and the authors wanted to see how such mutations are acquired and spread in an area with a relatively high prevalence of MDR and XDR strains. To date, however, MDR and XDR strains have been slower to grow, providing a line of defense against them. The researchers found that certain multidrug-resistant strains have managed to acquire additional mutations that overcome that slow growth, creating what the authors termed "a 'perfect storm," providing clinical drug resistance without compromising fitness and transmissibility." Those sobering findings appeared in the Jan. 26, 2014, advance online issue of *Nature Genetics*.

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We welcome your feedback. Contact Anette Breindl at anette.breindl@thomsonreuters.com, or (770) 810-3134.

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