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BUT HOW BIG'S THE MARKET?

Medivation, Astellas Pharma submit Xtandi sNDA for chemo-naïve PC

By Randy Osborne, Staff Writer

Medivation Inc. and partner Astellas Pharma Inc. made the latest move in the battle for prostate cancer marketing share by submitting a supplemental new drug application (sNDA) seeking a label for Xtandi (enzalutamide) in chemotherapy-naïve men.

Already cleared for marketing in the U.S. as a therapy against metastatic castration-resistant prostate cancer (mCRPC) patients who already have been treated with docetaxel, the androgen receptor inhibitor Xtandi continues to duke it out with Zytiga

See Medivation, page 3

Survey: EU physicians still face learning curve for biosimilars

By Mari Serebrov, Washington Editor

Biosimilar makers have their work cut out for them if they hope to increase the use of their follow-on biologics in Europe. Much of that work is in helping doctors over the learning curve.

Findings from a recent survey in France, Germany, Italy, Spain and the UK show that nearly a fourth of the 470

See Biosimilars, page 4

ASIA

Late-stage drug firms take more than half of China's VC pie

By Shannon Ellis, Staff Writer

SHANGHAI – In 2013, venture capital (VC) activity in China's life sciences sector remained strong, dipping only slightly below the year previous. Investor enthusiasm did not diminish even when

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IN THIS ISSUE

THE BIOWORLD BIOME

Dual cytokine targeting shows promise for pancreatic cancer

By John Fox, Staff Writer

HONG KONG – A biological extract that targets two proinflammatory protein pathways is showing promise against pancreatic cancer and may have potential for the management of several other malignancies, researchers said.

The fourth most common cause of cancer-related deaths in the U.S. and 12th worldwide, pancreatic cancer has a poor prognosis, with almost equal rates of incidence and mortality emphasizing the need for new targeted approaches for better management.

In China, pancreatic cancer is the sixth leading cause of death from malignancy, with an overall five-year survival rate of just 1 percent to 3 percent. As in Western countries, a major reason for that poor outcome is late diagnosis of the disease.

Extracts of the bark of the Amur cork

See Pancreatic cancer, page 6

NEWCO NEWS

Pain in the brain? Trigemina seeking to break the barrier

By Marie Powers, Staff Writer

No matter what the cause – cluster headaches, migraines, cancer, nerve damage, temporomandibular joint disorder, trigeminal neuralgia or another disorder – chronic head pain remains among the most vexing of medical conditions for patients and the most daunting of challenges for scientists. Over-the-counter remedies that may help acute conditions often are ineffective for chronic pain, and opioids that can relieve pain come with serious downsides.

Trigemina Inc. is seeking to resolve chronic head pain while sidestepping the dependency of opioid drugs by administering a new application of oxytocin to the nasal mucosa, where the drug migrates along cranial nerves and is delivered directly to the central nervous system.

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WASHINGTON ROUNDUP

Public Citizen and nine other groups are calling on President Barack Obama to veto the Gabriella Miller Kids First Research Act, which would create a new fund for pediatric research at the National Institutes of Health by transferring money from the Presidential Election Campaign Fund. "This is a fig-leaf bill whose only real intent is to whittle away at the presidential public financing program," said Craig Holman, government affairs lobbyist for Public Citizen. Although the Senate passed the bill unanimously March 11, following a House vote of 295-103 in December, the legislation had yet to show up by Tuesday on the White House list of bills awaiting presidential action. (See *BioWorld Today*, March 12, 2014.)

As part of its revision of a March 2003 guidance on bioavailability (BA) and bioequivalence (BE) studies for orally administered drugs, the FDA released a draft guidance on conducting BA and BE studies for investigational new drugs, new drug applications (NDAs) and NDA supplements. In addition to oral drugs, the guidance may be applicable to medicines administered through transdermal delivery systems, as well as certain rectal and nasal drugs. The draft was published in the *Federal Register* Tuesday. Comments are due by May 17.

FINANCINGS ROUNDUP

Achaogen Inc., of South San Francisco, said it closed its initial public offering of 6.9 million shares priced at $12 apiece, including the 900,000 shares sold as overallotments, resulting in gross proceeds of about $82.8 million. The company last month launched a pivotal phase III trial of lead antibacterial candidate plazomicin. Credit Suisse Securities (USA) LLC and Cowen and Co. LLC acted as joint book-running managers, while William Blair & Co. LLC and Needham & Co. LLC acted as co-managers. (See *BioWorld Today*, March 13, 2014.)

Agile Therapeutics Inc., of Princeton, N.J., said it filed a registration statement for a proposed initial public offering, though the number of shares and share price were not disclosed. Agile is developing contraceptive patches. RBC Capital Markets LLC and William Blair & Co. LLC are acting as joint book-running managers, while Cantor Fitzgerald & Co. and Jenney Montgomery Scott LLC are serving as co-managers.

Coming Thursday in *BioWorld Highlights*:

ROCK TO THE LEFT, HARD PLACE TO THE RIGHT: ONE DILEMMA OF COMPASSIONATE USE

Before its unfortunate drop in quality in its last few seasons, the medical drama *House* was one of my favorite shows, with its title character, a cranky, possibly drug-addicted doctor solving diagnostic riddles and saving lives with Sherlockian brilliance, and quite often breaking every rule in the book to do it.

To read more, see tomorrow's edition of *BioWorld Highlights*, a free weekly ezine that provides articles from *BioWorld Today*, *BioWorld Insight* and *BioWorld Asia*, plus insight and opinion from the *BioWorld Perspectives* blog, http://bioworld.blogs.bioworld.com. If you don't already receive this complimentary e-zine, click here to opt in.

STOCK MOVERS 3/18/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$68.30	+2.56%
Fate Therapeutics Inc.	+$1.08	+10.35%
Flamel Technologies SA	+$2.05	+18.40%
Geron Corp.	+$0.70	+39.33%
Omeros Corp.	+$1.22	+10.59%
Regado Biosciences Inc.	+$1.49	+12.41%

Biotechs showing significant stock changes Tuesday

BIOWORLD TODAY

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Medivation

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(abiraterone, Johnson & Johnson), an androgen biosynthesis inhibitor that is also given orally, but is dosed with prednisone.

Xtandi sold $392 million last year, but most investors have been slavering over the possibility of much bigger sales in the pre-chemo mCRPC space. With fewer side effects than Zytiga, Xtandi could have an edge, but nobody seems certain about the true size of the market.

Medivation could not be reached, but Medivation CEO David Hung, during a conference call on fourth quarter 2013 earnings, said that "while we've had to date an excellent launch of Xtandi based only on a post-chemo label, we believe that the upstream prostate cancer market, which is mostly managed by urologists, is largely untapped, given that the only drugs widely prescribed in those upstream indications are Lupron [leuprolide acetate for depot suspension, Abbott] and Casodex [bicalutamide, Astrazeneca plc]."

Use of the androgen receptor antagonists like Casodex dwarfs the use of CYP17 inhibitors such as ketoconazole in that population, so "we believe that, over time, Xtandi will be well poised to dominate this very commercially attractive market," Hung said.

In late January, San Francisco-based Medivation and Astellas, of Tokyo, disclosed phase III data from the PREVAIL trial, testing Xtandi in chemo-naïve patients, and those results were included in the sNDA package. (See *BioWorld Today*, Jan. 30, 2014.)

The results fell in line with interim data that had been disclosed the previous fall, and showed a statistically significant overall survival benefit compared with placebo, reducing the risk of death by 29 percent (HR = 0.71; $p < 0.0001$), compared with placebo, and the benefit held despite the use of subsequent therapies, at a rate of 40 percent in the Xtandi arm and 70 percent in the placebo group.

Xtandi cut the risk of disease progression by 81 percent (HR = 0.19; $p < 0.0001$) vs. placebo, too, and led to a 17-month delay in the time to start of chemo vs placebo (28 months with the drug vs. 10.8 months with placebo). Medivation and Astellas unveiled the PREVAIL outcomes at the American Society of Clinical Oncology's Genitourinary Cancers Symposium in San Francisco. But Zytiga has been tested in the chemo-naïve segment as well, also with satisfying results.

"Not surprisingly, data from PREVAIL are still filtering down into the community," Cowen and Co. analyst Eric Schmidt wrote in a research report Monday. His firm conducted its fourth urology survey of 32 U.S. urologists who treat about 10,000 patients altogether, and found that only 50 percent were familiar with PREVAIL's results.

"Nonetheless, PREVAIL seems to be impacting expectations for the pre-chemo market," Schmidt wrote. "For the first time in our survey series, Xtandi is projected to gain more market share in three years' time (37 percent) than Zytiga (30 percent). On the other hand, when prompted with the major efficacy findings of PREVAIL and Zytiga's COU-302 pre-chemo trial, a majority of physicians could either not pick a winner (38 percent) or viewed the drugs as having equal efficacy (17 percent). This may explain why Xtandi's projected lead over Zytiga is still fairly modest."

Other models coming out of Wall Street forecast much higher peak sales of Xtandi, with consensus U.S. sales set at almost $2 billion in 2017 vs. Zytiga's run rate of less than $1 billion.

HEAD-TO-HEAD AGAINST CASODEX

"With most urologists reporting that they are either already using Zytiga and/or Xtandi in pre-chemo patients (56 percent) or that they refer such patients to oncologists (25 percent) for treatment, we see limited opportunity for market growth," Schmidt wrote, adding that "physicians project that the average pre-chemo patient might be on Xtandi for just 14 months (similar to Zytiga), throwing into doubt [the notion of] market expansion driven by longer duration of dosing."

Cheryl Cohen, chief commercial officer, seemed to disagree during the conference call on fourth quarter 2013 earnings. "We do anticipate our duration to grow over time as we move upstream, and that's why it's so important that, once we get the PREVAIL label, and we're able to promote it," she said.

Bottom line for Schmidt is that Xtandi could reach worldwide sales of $3 billion to $4 billion. "Our valuation analysis is highly sensitive to changes in Xtandi's peak potential, but suggests [that] shares are about 20 percent over-valued, based upon our projections," he wrote.

Medivation's stock (NASDAQ:MDVN) closed Tuesday at $70.55, up $2.05.

Xtandi was approved in Europe last year for post-chemo mCRPC, and analysts expect approval as post-chemo therapy in Europe by the end of this year. Medivation and Astellas split U.S. profits down the middle, and Medivation gets royalties (estimated in the teens to low 20-percent range) on sales outside the country.

Medivation, during its earnings call in late February, said money will be invested in the pre-chemo push with Xtandi. Selling, general and administrative expenses will rise about 47 percent this year over 2013's numbers, mainly due to that effort, and head count will increase by 48 percent in support.

On the upside, Medivation is eligible under the terms of the Astellas deal for up to $552 million in regulatory and sales milestones, and expects to get $212 million of the $257 million development-milestone portion this year, including a $15 million milestone upon approval in Japan (for post-chemo patients) as well as milestones associated with pre-chemo filings and approvals.

Brean Capital Markets analyst Jonathan Aschoff, in a late February research report, conceded the "saturation of the post-chemo oncology market for Xtandi" but held out hope for the chemo-naïve opportunity, and maintained a "buy" rating on

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Biosimilars

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participating physicians didn't consider themselves familiar with biosimilars. And even though follow-ons have been marketed in the EU for almost eight years, 4 percent of the physicians said they had never heard of them.

At the other end of the curve, 22 percent of the doctors said they were "very familiar" with biosimilars and 54 percent thought they had a basic understanding of the drugs.

The steepness of the learning curve varied by country. For instance, 9 percent of the physicians surveyed in France had never heard of biosimilars, while only 2 percent in Italy and Spain were totally unaware of them. Likewise, 61 percent of the French physicians expressed at least some basic understanding of the drugs, compared with 87 percent in Spain and 83 percent in Italy.

The physicians who participated in the survey were evenly divided among the five countries and within the practice areas of dermatology, endocrinology, neurology, nephrology, oncology and rheumatology; 92 percent prescribe biologics in their practice.

The survey, conducted by Industry Standard Research and sponsored by the Alliance for Safe Biologic Medicines (ASBM), also shows a lack of awareness of the EMA approval path for biosimilars. Nearly 40 percent of the prescribers were unaware that clinical trials for one indication could lead to marketing authorization of a biosimilar for other indications.

"Doctors need to be fully aware of the characteristics of biologics and biosimilars to be in a position to prescribe the medicine that will maximize patient outcomes," Nathalie Moll, secretary general of EuropaBio, said when the survey results were presented. The trade group plans to raise that awareness in the coming months through an open dialogue with physicians and regulators at workshops throughout the EU.

CLINICAL PERSPECTIVE ON NAMING

The findings from the first large-scale survey on biosimilars in the EU also reflect "the daily clinical practice with regards to biologic medicines including biosimilars and [provide] facts and figures that put current international, EU as well as national policy developments in the field of naming and substitution into perspective," ASBM Executive Director Michael Reilly said.

When it comes to drug names, 61 percent of the doctors said if two biologics have the same international nonproprietary name (INN), they are approved for the same indications; 53 percent considered them structurally identical. Nearly half the doctors said either drug could be used with the same result, and 39 percent thought they could be safely switched during treatment with the same result.

Nearly all the physicians said they identify drugs they prescribe in patient records. While about a third identify the drugs by both brand and INN, 30 percent record only the brand name, whereas 24 percent use only the INN.

The practice varies by country. In the UK, 37 percent use the INN in the patient record and 30 percent use both, but 53 percent of the doctors in France and 40 percent of those in Germany record only the brand name. In Spain, 37 percent use both and 36 percent rely on the INN. In Italy, 42 percent record both, with 27 percent using just the brand name and 25 percent using the INN.

In reporting adverse events, more than half the physicians give both the brand name and INN, with 29 percent using only the brand name and 17 percent using the INN. Again, the practice varies by country. Whereas 70 percent of the doctors in Spain report both names for adverse events, 58 percent of those in France report only the brand name, while 32 percent use both and 10 percent give the INN.

ASBM, which has spoken out on the need for distinct INNs, concluded that the survey findings show that the "use of distinguishable INN for all biologics, including biosimilars, is critical to further strengthen and facilitate patient safety through effective pharmacovigilance." (See *BioWorld Today*, May 14, 2012.)

VIEWS ON SUBSTITUTION

As for what a pharmacy dispenses, the majority of physicians in all five countries thought they should be able to indicate that no drug substitutions are to be made and they want to be notified when there is a substitution for patients needing long-term treatment. Nearly 80 percent of the doctors considered notice of substitution as "very important" or "critical" for patients with chronic conditions that require ongoing therapy, and 16 percent viewed it as "somewhat important."

If pharmacy substitutions were an option in their country, 74 percent of the doctors said it would be "very important" or "critical" for them to have the authority to designate a biologic medicine as "dispense as written" or "do not substitute." Likewise, 72 percent thought it "very important" or "critical" for them to have the sole authority to decide, together with their patients, the most suitable biologic for each patient.

When asked their views on biologic (innovator and biosimilar) substitution at the beginning of treatment, 62 percent of the physicians said it's not acceptable. However, 35 percent said it would be acceptable if they have an agreement with the pharmacists in advance as to which biologics could be substituted. //

Medivation

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Medivation's stock.

Two phase II trials also are under way, called TERRAIN and STRIVE, testing Xtandi head-to-head against Casodex. In July of last year, Astellas completed targeted patient enrollment in the TERRAIN trial, which enrolled about 370 men with mCRPC, mainly in Europe. STRIVE aims to enroll about 400 patients, with metastatic or nonmetastatic disease, mostly in the U.S. //

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VC

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China barred companies from holding initial public offerings (IPOs) here, the exit of choice for VCs.

That was the assessment of Chinabio LLC, a China-based consulting firm that tracks deals in China's life sciences, in its recent report, *China Investment 2014: Reform and Transformation*.

"Depending on how you measure VC or private equity [PE] investment performance, 2013 was a solid year, but did not surprise," said the report's authors.

Greg Scott, president of Chinabio, told *BioWorld Asia* there are still a few eye openers lurking behind the numbers.

The number of VC life sciences deals increased from 33 in 2012 to 42 in 2013 even though the total deal value went down 10 percent, from $986 billion to $901 billion.

But Scott cautioned that those numbers only reveal the publicly available VC investments, and in China he estimated a fraction are announced, with or without deal terms. By his estimate, there are some 150 to 200 VC/PE deals a year in total.

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OTHER NEWS TO NOTE

Bioatla LLC, of San Diego, and **Telephus Medical LLC**, also of San Diego, which develops vaccine products to prevent periprosthetic joint infections, said Bioatla completed a protein engineering phase of Telephus' compound, TPH 101, which is focused on the development of neutralizing antibodies targeting a key bacterial enzyme that drives the formation of antibiotic-resistant biofilm infections on implanted medical devices. Under the firms' collaboration, Bioatla is eligible for milestones and royalty payments upon commercialization of TPH 101.

Biogen Idec Inc., of Cambridge, Mass., said the FDA extended the initial PDUFA data for its review of the biologics license application for Plegridy (peginterferon beta-1a) in multiple sclerosis. The PDUFA date has been extended by three months, which is the standard extension period, because the agency needs more time.

Calithera Biosciences Inc., of South San Francisco, reported preclinical data on the activity of CB-839, a selective, orally available glutaminase inhibitor, in solid and hematologic tumor types, with triple-negative breast cancer cell lines markedly more sensitive to CB-839 than ER-positive cell lines. Sensitivity also was directly correlated to the level of glutaminase expression and the baseline ratio of glutamate to glutamine prior to drug treatment. Those and other data were presented at the Keystone Symposium on Tumor Metabolism in Whistler, British Columbia.

Effrx Pharmaceuticals SA, of Zurich, said it established a collaboration with **Kadmon Corp. LLC**, of New York, under which Effrx will generate effervescent formulations to be developed by Kadmon in both adult and pediatric orphan indications. Financial terms were not disclosed.

Galapagos NV, of Mechelen, Belgium, reported preclinical data showing that GLPG1790, a selective small-molecule inhibitor of the ephrin receptor kinase family, could play a role in melanoma, pancreatic, ovarian, prostatic and colorectal cancers, as well as in triple-negative breast cancer (TNBC). The drug showed in vivo efficacy in a TNBC xenograft model, with full tumor blockage observed after 30 mg/kg oral dosing, which correlated with target inhibition in the tumor.

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Pancreatic cancer

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tree, *Phellodendron amurense*, have long been used effectively in traditional Chinese medicine (TCM) for treating a wide range of illnesses, including pneumonia, tuberculosis and liver cirrhosis, which share certain similar characteristics to cancer.

"There have been a number of anticancer agents derived from plants," noted Brian Tomlinson, professor of medicine and therapeutics and head of the Division of Clinical Pharmacology at the Chinese University of Hong Kong. "Good examples are the taxanes, paclitaxel (Taxol) and docetaxel (Taxotere), which were originally derived from the bark of the yew tree," he told BioWorld.

Addanki Pratap Kumar, a researcher at the University of Texas Health Science at San Antonio, already was exploring the extract, available in the U.S. as a dietary supplement called Nexrutine, in treating prostate cancer when his team found that pancreatic cancers shared similar pathogenic pathways with prostate tumors.

Kumar's initial interest in Nexrutine in prostate cancer had arisen when Next Pharmaceuticals Inc., of Salinas, Calif., the company that manufactures and sells Nexrutine in the U.S., reported reduced levels of prostate-specific antigen, a marker for the malignancy, in men taking the supplement for relieving joint pains.

"I was intrigued about this correlation and, given my interest in the use of natural products for cancer management, I began working with Nexrutine," Kumar told BioWorld.

Nexrutine contains the potent alkaloids berberine and protoberberine-like compounds, which are used in TCM for their antibiotic properties. "In our experience, three of these compounds exhibit cytotoxic activity," Kumar said. "However, at this time, we believe it may be important to have all the components in the mixture."

In a paper published in the latest issue of *Clinical Cancer Research*, Kumar and his team demonstrated that the extract blocks two proinflammatory protein pathways, inhibiting the scarring or fibrosis that impairs the efficacy of cancer drugs.

Testing of Nexrutine in a range of experimental pancreatic cancer cells showed that the extract reduced levels of two protein pathways contributing to fibrosis in those tumors, called NF-κB and STAT3, which promote cyclo-oxygenase-2 (Cox-2), an enzyme that also causes inflammation and fibrosis. Nexrutine also appears to suppress that enzyme.

"Fibrosis is a process of uncontrolled scarring around the tumor gland," said Kumar, the study's principal investigator. "Once you have fibrotic tissue, the drugs cannot get into the cancer."

However, fibrosis alone is unlikely to be the only factor affecting cancer drug efficacy, Tomlinson pointed out, since "cancers are often well supplied with blood vessels, so macroscopic fibrosis [alone] may not limit the entry of anticancer agents."

Nevertheless, Kumar noted that in addition to prostate and pancreatic cancers, liver and kidney tumors also develop fibrosis and resistance to drugs and that there currently are no chemotherapies targeting that inflammatory pathway in those cancers. The potential of natural substances to treat disease is appealing, but the main advantage of natural compounds such as cork tree extract, which is available over the counter in the U.S. in capsule form, is that it is presumed to have been shown safe for use in patients.

However, "although we obtained Food and Drug Administration approval to use Nexrutine for one clinical study, we do not know the definitive doses for medical use at this time," Kumar said.

In a promising prostate cancer clinical study led by Kumar, which is testing Nexrutine in 24 patients, all patients tolerated the treatment well, he said. Now the researchers are analyzing the results and, with more funding, plan to expand the study to a much larger group of patients.

Meanwhile, the complex interrelationship between the two protein signaling pathways that contribute to fibrosis in those tumors and promote Cox-2 remains "the million-dollar question," Kumar said. Solving that question is one of the next steps in his research.

"This work is just the tip of the iceberg," he said, noting that cancer is a complex disease and cancer cells are constantly finding ways to survive. "Over the years, we have learned that shutting down one pathway will only allow cancer cells to find other ways to survive," he said.

"This is one of the reasons we are excited about Nexrutine – because the bark extract . . . contains many compounds, it can shut down multiple pathways simultaneously so that the cancer cell is attacked on multiple fronts.

"We are actively testing other mechanisms that Nexrutine can target, as well as testing individual components in combination with existing chemotherapeutic agents to determine if such combinations can reduce the toxicity associated with chemotherapeutic agents." //

FINANCINGS ROUNDUP

Aldeyra Therapeutics Inc., of Burlington, Mass., (formerly Aldexa Therapeutics) set terms for its proposed initial public offering of 2 million shares priced at a range of $10 to $12 per share. At the midpoint, the company would bring in $22 million to fund its pipeline for rare skin and eye diseases. (See *BioWorld Today*, Jan. 8, 2014.)

Dipexium Pharmaceuticals Inc., of New York, said it closed its initial public offering of about 3.2 million shares priced at $12 apiece, including 412,500 shares to cover overallotments. Gross proceeds totaled about $38 million. Dipexium said net proceeds of about $35.1 million will be used to further develop Locilex (pexiganan acetate cream 1 percent) for mild infections of diabetic foot ulcers, including pivotal phase III studies, as well as for working capital and general corporate purposes. Oppenheimer & Co. acted as sole book-running manager, while Feltl and Co. acted as co-lead manager.

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Trigemina

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The Moraga, Calif.-based company was founded in 2006 by David Yeomans, director of pain research and associate professor of anesthesia at Stanford University School of Medicine, and the company's chief scientist. Some months earlier, Yeomans had struck up a conversation at a conference with William Frey, founder and co-director of the Alzheimer's Research Center at Regions Hospital, professor of pharmaceutics and a faculty member in neurology, oral biology and neuroscience at the University of Minnesota. Frey had discovered a non-invasive, intranasal method for bypassing the blood-brain barrier to rapidly deliver and target therapeutic agents to the brain along the olfactory and trigeminal neural pathways – thus, the company's name. Yeomans thought the method could prove an ingenious route for delivering large molecules to the brain to provide an analgesic effect.

The two began running experiments, which showed impressive results using oxytocin, according to Charles Yeomans, David's brother, who now serves as Trigemina's CEO. The scientists filed patents based on David Yeomans' work at Stanford and continued to conduct preclinical and early clinical experiments. In the lab, they showed the application of oxytocin, using Frey's delivery method, halted the effect of calcitonin gene-related peptide, or CGRP, the neurotransmitter for pain. The process worked even to tamp down migraine, with its constellation of symptoms.

In 2007, the company conducted a phase II trial in Australia, administering a single dose in acute migraine patients as soon as possible after the onset of symptoms. The mechanism of action was not well understood at the time, however, according to Charles Yeomans, who explained that a certain amount of time was needed following the onset of migraine to up-regulate the receptor and induce inflammation, providing a target for the drug to do its job. Too, it was critical for patients to avoid the use of any substance that might potentially prevent that up-regulation process. Long story short, the initial efficacy trial fell flat.

The scientists went back to the drawing board and, in 2009, conducted a smaller trial in 40 patients with chronic migraine, "who were more likely to be up-regulating all the time," Charles Yeomans said. This time, the oxytocin delivery method worked better, but the company ran out of money before it could repeat the experiments and study the long-term effects of the drug.

Charles Yeomans, who had a background in banking and private equity investment and was an early investor in Trigemina, offered to step in so his brother could keep the research team together. The new CEO attracted venture funding from Chilean-based investor Aurus, through its Aurus Bios Fund, supplemented by additional funding from high net worth individuals. In late 2011, Trigemina was "reconstituted," Yeomans said.

'WE DON'T WANT TO HAND THIS OFF AND WALK AWAY'

Work on the intranasal oxytocin candidate, TI-001, has progressed rapidly ever since. In May 2013, the company began a randomized, double-blind, placebo-controlled, withdrawal- and enrollment-enriched phase II safety and efficacy study using the nasal spray formulation. The study is expected to enroll 240 chronic migraine patients in Chile and Australia.

The primary outcome measure is mean reduction in migraine headache days from baseline – the 28-day screening period before enrollment in the study, according to Thomson Reuters Cortellis Clinical Trials Intelligence (CTI). Secondary measures include frequency of migraine episodes; change in migraine pain scores; frequency and severity of adverse events; frequency of nausea, phonophobia and photophobia; time to discontinuation due to any cause; and interleukin-6 levels as a marker of response, according to Cortellis CTI. The study also is assessing several doses, from 15 to 60 IU, to determine the best dose for a phase III study.

In June 2013, Trigemina completed a $4.5 million series A financing, led by Aurus and supplemented by a grant from the government of Chile, to fund the phase II study to completion. The company expects to report data late in the third quarter.

"If the early trends hold, we will have a very strong candidate to help chronic migrainers," Yeomans said. "We think this will be a candidate to move into phase III pretty fast."

Migraine is a large but challenging space dominated by Botox (onabotulinumtoxinA, Allergan Inc.). In January 2013, Allergan moved to secure its position in migraine treatment by purchasing MAP Pharmaceuticals Inc. in a cash deal, acquiring the company's shares at $25 each. (See *BioWorld Today,* Jan. 24, 2013.)

In December 2013, Depomed Inc. added some interest to the space and boosted its pain portfolio with the purchase of Nautilus Neurosciences Inc.'s migraine drug, Cambia (diclofenac potassium for oral solution) – the only single agent nonsteroidal anti-inflammatory specifically indicated for migraine. (See *BioWorld Today*, Dec. 19, 2013.)

But chronic migraine remains unchartered territory, though a growing number of companies is seeking to fill the void, with CGRP receptor antagonists among the leading mechanisms of action. Once the TI-001 phase II is complete, Trigemina likely will seek another financing round to move post haste into phase III, Yeomans said.

Trigemina has a second molecule, TI-002, a polypeptide also delivered via the nasal-cerebral pathway that is designed to target a broad range of pain throughout the body, including neuropathic pain.

With multiple assets, the company's long-term business strategy will depend on the circumstances.

"If we complete our trial, we could look for a partner that would be supportive and help us to get this into the market," Yeomans

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Trigemina

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said. "But with the expertise we've developed internally, we don't want to hand this off and walk away. We have a lot of passion for this drug, and we want to see it get to people whom it could help." //

FINANCINGS ROUNDUP

Galmed Pharmaceuticals Ltd., of Tel Aviv, Israel, said it closed its initial public offering of about 3.3 million shares priced at $13.50 per share, which included 425,610 shares issued to cover overallotments. Gross proceeds totaled about $44.1 million, and net proceeds are expected to be about $39.7 million. Galmed intends to use funds for clinical trials and product development, including about $10 million for the initiation and completion of a phase IIb trial testing aramchol in nonalcoholic steatohepatitis in patients who also suffer from obesity and insulin resistance. Maxim Group LLC acted as sole book-running manager, while MLV & Co. and Feltl and Co. acted as co-managers.

Ignyta Inc., of San Diego, said underwriters exercised their full overallotment option to purchase an additional 786,750 shares of common stock at the initial public offering (IPO) price of $9.15 per share, bringing gross proceeds from the IPO to about $55.2 million. Net proceeds, expected to total about $51.3 million, will be used for a planned phase I/II trial of RXDX-101, an oral tyrosine kinase inhibitor, in metastatic cancer with relevant molecular mutations. (See *BioWorld Today*, March 17, 2014.)

Ovascience Inc., of Cambridge, Mass., said underwriters exercised their option to purchase an additional 518,630 shares of common stock at the offering price of $10 per share, bringing the public offerings' total gross proceeds to $55.2 million. Funds are expected to support the firm's pipeline of fertility therapies, including Ovaprime and Augment, and for working capital and other general corporate purposes. Leerink Partners LLC acted as sole book-running manager, while co-managers included Cantor Fitzgerald & Co., H.C. Wainwright & Co. LLC, JMP Securities LLC, Ladenburg Thalmann & Co. and Roth Capital Partners. Separately, the company's CEO, Michelle Dipp, Chairman Richard Aldrich and board member Harald Stock set up 10b5-1 plans to purchase Ovascience common stock in the open market.

Oxygen Biotherapeutics Inc., of Morrisville, N.C., said it priced a public offering at $5.60 per share, a 9.8 percent discount to Monday's closing price, for gross proceeds of about $52 million. The company also granted underwriters a 45-day option to purchase an additional 1.4 million shares to cover overallotments, which could bring in another $7.8 million. Net proceeds are expected to advance the firm's clinical trials and efforts to obtain regulatory approval for Levosimendan and Oxycyte, develop other product candidates, support manufacturing initiatives, fund R&D and for other general corporate purposes. Ladenburg Thalman & Co. Inc. is acting as the sole book-running manager, while MTS Securities LLC is acting as co-manager for the offering, set to close on or about March 21. The offering followed news earlier this month that the FDA had lifted the clinical hold on Oxycyte, a perfluorocarbon therapeutic oxygen carrier in development for traumatic brain injury. Shares of Oxygen (NASDAQ:OXBT) lost 53 cents to close Tuesday at $5.68. (See *BioWorld Today*, March 5, 2014.)

OTHER NEWS TO NOTE

Geron Corp., of Menlo Park, Calif., is the subject of a class action lawsuit by Levi & Korsinsky in U.S. District Court for the Northern District of California on behalf of investors who bought stock between June 16, 2013, and March 11, 2014. The complaint alleges that Geron misrepresented and/or failed to disclose that: (a) persistent low-grade liver function test abnormalities had been observed in the phase II study of its drug imetelstat in essential thrombocythemia or polycythemia vera patients; (b) there was a high risk of potential chronic livery injury following long-term exposure to the drug; and (c) as a result of the foregoing, defendants' positive statements about the prospects for imetelstat lacked a reasonable basic and/or were materially false and misleading. The lead plaintiff deadline is May 13, 2014. (See *BioWorld Today*, March 13, 2014.)

Lipocine Inc., of Salt Lake City, has been approved to begin trading on Nasdaq on or about March 21, under the trading symbol LPCN.

Novogen Ltd., of Sydney, and its joint venture company with Yale University, **Cantx Inc.**, of New Haven, Conn., disclosed a milestone with lead candidate drug, Trx-1, demonstrating a potent anticancer effect in mice xenografted with human ovarian cancer stem cells. Cantx is seeking a new approach to the treatment of abdominal cancers by developing a product to be administered intraperitoneally with the ability to seek out tumor cells and to eliminate the full hierarchy of cells within tumors. The final product is envisaged to be Trx-1 in a "smart" drug delivery system, the company said.

Specialised Therapeutics Australia Ltd., of Melbourne, said Abraxane (nanoparticle albumin-bound paclitaxel) in combination with gemcitabine was approved in Australia for the first-line treatment of metastatic pancreatic cancer. The product gained FDA approval last year and is sold in the U.S. by **Celgene Corp.**, of Summit, N.J. (See *BioWorld Today*, Sept. 9, 2013.)

Transgene SA, of Strasbourg, France, said the acquisition of partner **Jennerex Inc.**, of San Francisco, by **Sillajen Inc.**, of Busan, South Korea, has been completed. (See *BioWorld Today*, Nov. 27, 2013.)

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OTHER NEWS TO NOTE

Zymeworks Inc., of Vancouver, British Columbia, and the National Research Council of Canada (NRC) inked a collaboration to focus on developing therapies for cancer, as well as for inflammatory and autoimmune diseases. The three-year, multimillion-dollar agreement will provide Zymeworks access to NRC's expertise, scientific facilities and know-how to complement the firm's capabilities in the development and deployment of products for local and international markets in areas of significant unmet medical need. Specific financial terms were not disclosed.

CLINIC ROUNDUP

Acceleron Pharma Inc., of Cambridge, Mass., said partner **Celgene Corp.**, of Summit, N.J., will present interim data from an ongoing phase IIa study of sotatercept in patients with end-stage renal disease (ESRD) on hemodialysis at the National Kidney Foundation 2014 Spring Clinical meeting in April. The data to be presented are from a dose-escalation study of sotatercept administered subcutaneously every 28 days to evaluate the pharmacokinetics, safety, tolerability, efficacy and pharmacodynamics of the drug for the correction of anemia in patients with ESRD on hemodialysis. Following a single dose in the placebo, sotatercept 0.3 mg/kg and sotatercept 0.5 mg/kg dose groups, peak mean hemoglobin changes observed in the first 28 days were 0.1 g/dL, 0.5 g/dL and 0.8 g/dL, respectively. Adverse events were mostly mild to moderate, unrelated to study drug and generally consistent with patients' medical histories. No dose-dependent changes in blood pressure were observed. The trial is being conducted at sites in the U.S. and may enroll up to 56 patients.

Alcobra Ltd., of Tel Aviv, Israel, said the first patient has been enrolled in a phase III trial of metadoxine extended release (MDX) in the treatment of adults with attention deficit hyperactivity disorder (ADHD). The 300-patient study will be conducted at 20 sites in the U.S and Israel. Patients will be randomized to receive either 1,400 mg MDX or placebo over six weeks following a two-week screening period. The primary endpoint is the Conners' Adult ADHD Rating Scale (CAARS-INV), a widely accepted clinical measure of the presence and severity of ADHD symptoms. Secondary endpoints will include the computerized TOVA (Test of Variables of Attention) which also was used in the previous phase II studies, as well as additional exploratory endpoints.

Antisense Therapeutics Ltd., of Victoria, Australia, said it started dosing in its phase I stem cell mobilization (SCM) human proof-of-concept trial of ATL1102, its second-generation antisense drug targeting the VLA-4 receptor. The trial will assess the safety, tolerability and effect of ATL1102 on the release of hematopoietic stem cells (CD34-positive) into the blood when dosed alone and in combination with an existing therapy (granulocyte colony stimulating factor). The product will be dosed over five days (given on days 1, 3 and 5) in 10 healthy volunteers. It is anticipated that the results will be reported midyear.

Cerulean Pharma Inc., of Cambridge, Mass., said the first patient was dosed in a phase Ib/II trial designed to identify the recommended phase II dose of CRLX101 in combination with Xeloda (capecitabine, Roche AG) and radiation and to detect signals, if any, of increased efficacy over standard neoadjuvant chemoradiotherapy for rectal cancer. The open-label, single-arm, investigator-initiated trial is expected to enroll up to 53 patients. The primary endpoint is pathologic complete response rate, with secondary endpoints of safety, disease-free survival and overall survival. CRLX101 is a dual inhibitor of hypoxia-inducible factor-1a and topo 1 that has shown synergy with radiotherapy and VEGF inhibitors, including Avastin (bevacizumab, Roche AG), in preclinical models. Last week, the biotech filed with the SEC seeking to raise up to $75 million through an initial public offering designed to fund studies of CRLX101 in other indications after a miss in advanced non-small-cell lung cancer. (See *BioWorld Today*, March 25, 2013, and March 11, 2014.)

Genspera Inc., of San Antonio, said the first patient was enrolled in the phase II trial of its lead compound, G-202, in patients with glioblastoma multiforme (GBM). The trial is expected to treat up to 34 patients with GBM that has progressed or recurred after at least one other treatment, including surgery and/or radiotherapy. The primary endpoint is six-month progression-free survival after at least two cycles of treatment. Phase II trials of G-202 also are under way in hepatocellular carcinoma and glioblastoma. (See *BioWorld Today*, Sept. 13, 2010.)

Igenica Biotherapeutics Inc., of Burlingame, Calif., said the first patient was dosed in a phase I trial of IGN523 in patients with relapsed or refractory acute myeloid leukemia (AML). The trial is assessing the safety, pharmacokinetics and clinical activity of the company's lead antibody, which targets CD98, a cell surface protein frequently overexpressed on AML cells. (See *BioWorld Today*, June 13, 2012.)

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CLINIC ROUNDUP

Ironwood Pharmaceuticals Inc., of Cambridge, Mass., said dosing has begun in a phase IIa study of investigational compound IW-3718, a gastric retention formulation of a bile acid sequestrant co-developed with **Depomed Inc.**, of Newark, Calif., through incorporation of its Acuform drug delivery technology, in patients suffering from gastroesophageal reflux disease (GERD) who have not responded adequately to treatment with a proton pump inhibitor (PPI). The trial is expected to enroll approximately 90 patients with a confirmed diagnosis of GERD who are taking a PPI and continuing to experience GERD symptoms. Patients will continue to take their PPIs with the addition of either IW-3718 or placebo. The exploratory phase IIa trial will evaluate a number of different GERD symptoms and efficacy endpoints, as well as safety and tolerability of IW-3718. Data are expected in the first half of 2015. Preliminary findings from nonclinical studies conducted by the company and its collaborators have shown that bile acids can cause relaxation of the lower esophageal sphincter, which allows reflux of contents from the stomach into the esophagus. Bile and bile acids also were shown to cause increased activity of esophageal nerve fibers in related nonclinical studies. Importantly, those study data suggest that a bile acid sequestrant may be able to block those actions.

Pharma Two B Ltd., of Rehovot, Israel, said it began enrolling patients in a phase IIb study of its fixed-dose combination product, P2B001, to treat the early stages of Parkinson's disease (PD). The multicenter, randomized, double-blind, placebo-controlled, parallel group study is designed to determine the safety, tolerability and efficacy of two doses of once-daily P2B001 for 12 weeks in 150 patients with early PD. The company is following the FDA's 505(b)(2) registration pathway for the compound, which combines two drugs with a complementary mechanism of action in a slow release formulation. Pharma Two B also said findings from the phase I, four-way comparative pharmacokinetics (PK) study of P2B001 showed there were neither PK interactions between the components or unexpected adverse effects.

Prosensa Holding B.V., of Leiden, the Netherlands, reported encouraging 48-week data from its U.S.-based, phase II placebo-controlled study (DMD114876 or DEMAND V) of its lead compound, drisapersen, for the treatment of Duchenne muscular dystrophy (DMD), at the Muscular Dystrophy Association Clinical Conference. The results indicated that, compared to placebo, boys in the higher-dose drisapersen group (6 mg/kg once weekly) experienced stabilization and even improvements in their muscle function and physical activity as measured by the six-minute walk test (6MWT) for the 24-week treatment phase and maintained that improvement during the 24-week follow-up period. Additionally, when evaluating the percent-predicted six-minute walk distance, a clinically meaningful treatment difference of 5.2 percent was observed at week 24 and 4.8 percent at week 48. The study included 51 boys with DMD who were at least 5 years old, still able to walk and stand up from the floor without help in less than 15 seconds.

Summit Corp. plc, of Oxford, UK, said the FDA cleared its investigational new drug (IND) application for a phase II proof-of-concept study of its antibiotic, SMT19969, to treat *Clostridium difficile*. The submission of that application has resulted in a £1.9 million (US$3.2 million) milestone payment by the Wellcome Trust to support the study. An oral small-molecule antibiotic, SMT19969 previously demonstrated safety, tolerability and high selectivity for *clostridia* only in a phase I study in healthy volunteers. The phase II trial, named CoDIFy, will be a double-blind, active-controlled trial comparing the efficacy of SMT19969 to standard-of-care vancomycin in 100 *C. diff* patients by assessing both initial cure rates and absence of recurrent *C. diff* infection within 30 days of the end of treatment. The trial is expected to begin enrolling during the first half of the year.

PHARMA: CLINIC ROUNDUP

Ipsen SA, of Paris, reported phase IIa results showing that Dysport was associated with a mean reduction from baseline of urinary incontinence episodes greater than 75 percent, 12 weeks after injection, regardless of how the drug was administered in patients with urinary incontinence not adequately managed by anticholinergics. Results were achieved with a single dose injected in either 15 or 30 sites in the detrusor muscle. Dysport is an injectable form of botulinum toxin type A.

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