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10-5, WITH ONE ABSTENTION

FDA's AMDAC supports Merck's bezlotoxumab for *Clostridium difficile* drug – with reservations

By Mari Serebrov, Regulatory Editor

Although the FDA's Antimicrobial Drugs Advisory Committee (AMDAC) voted 10-5, with one abstention, that Merck & Co. Inc.'s bezlotoxumab showed substantial evidence of safety and efficacy in preventing the recurrence of *Clostridium difficile* infection (CDI), Thursday's vote was far from a slam dunk victory.

Whether they voted yes or no, the panelists expressed several concerns about the first-in-class drug designed to neutralize *C. difficile* toxin B. Most of them stemmed from a desire for more data and questions about which patients would benefit from

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BIO 2016

Will biopharma deal-making brave the headwinds or retreat to 'wait-and-see'?

By Marie Powers, News Editor

Following a record-breaking year for deal-makers, 2016 isn't exactly off to the races. The drug pricing debate, magnified through the lens of a contentious Presidential campaign, and

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DEALS AND M&A

Sorrento, 3SBio ink CAR T JV in China

By Shannon Ellis, Staff Writer

SHANGHAI – Shenyang Sunshine Pharmaceutical Co. Ltd. (3SBio), a revenue-generating biotech with products in China, has decided to try its hand at the hottest category in immuno-oncology. The company will be responsible for developing three chimeric antigen receptor T cell (CAR T) candidates in Greater China (including Macao and Hong Kong) originally

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PRECISION MEDICINE

Is China's precision medicine initiative a foreign affair?

By Cornelia Zou, Staff Writer

HONG KONG – Although the government has set its sights on advancing personalized medicine in China, most of the existing gene-related technologies are still of foreign origin,

See Precision, page 6

ALLICENSE 2016

Platform party: Resurging interest spurs more deals, but terms call for caution

By Randy Osborne, Staff Writer

SAN FRANCISCO – "Platforms are 'in' again," said Arthur Sands, CEO of Nurix Inc., which last September bagged an agreement with Celgene Corp. that brought $150 million up front plus an undisclosed equity investment to discover and develop drugs that target the ubiquitin proteasome system (UPS). "They were 'out' for a long time, and I think it's scientifically very exciting and appropriate, given the recent advances in all sorts of areas," such as chimeric antigen receptor T cells in immuno-oncology and protein homeostasis approaches. Megatrends offer "great opportunity to do very large deals around that science and technology" in order to scale up efforts, he said. "You're not going to be able to raise enough capital in the markets, nor would you necessarily want to."

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IN THIS ISSUE

THE BIOWORLD BIOME

Parasites worm their way into arthritis treatment

By John Fox, Staff Writer

HONG KONG – The findings of a new collaborative study by Chinese and German scientists suggest that activation in mice of a specific type of immune response, known as a Type 2 (Th2) response, using parasitic worm-derived stimuli, could clear the way to

See Arthritis, page 8

REGULATORY FRONT

As part of the ninth annual International Internet Week of Action, the **FDA**, in partnership with international regulatory and law enforcement agencies, took action this week against 4,402 websites that illegally sell potentially dangerous, unapproved prescription drugs to U.S. consumers. The annual global cooperative effort is led by **INTERPOL** and targets the online sale of illegal and counterfeit drugs.

FDA and **Health Canada** regulatory pressures factored into a 24-hour strike and subsequent lockout at a **Sandoz Canada** plant in Boucherville, Quebec, this week. Teamsters Canada called the strike Tuesday, citing "the many extra duties imposed on them due to increasingly complex and stringent standards issued by Canadian and U.S. regulators." Regulatory requirements and a poor work atmosphere have created a climate of fear at the plant, which also is plagued by high turnover among senior management and supervisors, the union said. When workers showed up Wednesday, they were turned away. Sandoz Canada, part of the Basel, Switzerland-based Novartis Group, produces injectable drugs used in hospitals and long-term care centers. It also distributes antibiotics, lyophilized products and other drugs.

FINANCINGS

CTD Holdings Inc., of Alachua, Fla., said it closed a private placement of its securities with investors purchasing 8 million units at $0.25 each. Each unit consisted of one share of common stock and one seven-year warrant to purchase one share of common stock at an exercise price of $0.25. The proceeds will support the company's drug development program of Trappsol Cyclo in the treatment of Niemann-Pick Type C, a rare genetic disease which causes neurologic, liver and lung dysfunction and is ultimately fatal.

Sarepta Therapeutics Inc., of Cambridge, Mass., said it intends to sell an amount of its common stock equal to approximately $37.5 million in gross proceeds in an underwritten offering. The company intends to use the net proceeds principally for product and commercial development, manufacturing, any business development activities and other general corporate purposes.

Selecta Biosciences Inc., of Watertown, Mass., has filed with the SEC to offer 4.25 million shares, priced between $14 and $16 each in an IPO. The company said it is using synthetic vaccine particle technology to discover and develop targeted therapies that are designed to modulate the immune system to effectively and safely treat rare and serious diseases. They have applied to list their common stock on the Nasdaq Global Market under the symbol SELB.

OTHER NEWS TO NOTE

Accel-Rx, of Vancouver, British Columbia, and its partner BDC Capital, said they have invested C$1.8 million (US$1.4 million) in **Imstar Therapeutics Inc.**, also of Vancouver, which is working on a new approach to treat amyotrophic lateral sclerosis patients. The infusion of capital will allow Imstar to continue with the necessary preclinical work required before moving on to clinic trials, including pharmacology and dose-ranging studies.

IN THE CLINIC

Acorda Therapeutics Inc., of Ardsley, N.Y., reported that during a phase I intra-patient, single ascending dose trial of its inhaled zolmitriptan candidate, CVT-427, it found oral and nasal spray formulations had a median Tmax of 1.5 hours and 3 hours, respectively vs. a median Tmax of 0.17 hours for all four dose levels of CVT-427. The mean Cmax for the oral formulation was 8.7 ng/mL, and the nasal spray formulation was 8.1 ng/mL. The mean Cmax values for CVT-427 were 6 ng/mL (0.825 mg dose), 11.8 ng/mL (1.65 mg), 17.8 ng/mL (3.0 mg), and 35.0 ng/mL (6.0 mg). There were no serious adverse events, dose limiting toxicities, or study discontinuations due to adverse events reported. The data is being presented today at the Annual Scientific Meeting of the American Headache Society in San Diego.

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Merck

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the fully human monoclonal IgG1/kappa antibody.

"This is not a rare disease," AMDAC Chairman Lindsey Baden, director of the clinical research division of infectious diseases at Brigham and Women's Hospital, said as he explained his no vote. Thus, it shouldn't have been difficult to conduct studies in large populations to determine who would best benefit from the drug, he added. Baden was uncomfortable that a novel drug for what could be a large, new indication was tested in only 800 patients in the two phase III trials.

While the data Merck served up were intriguing, Baden said the sponsor "was not there yet." He suggested the phase III trials were more like phase IIb trials.

Ellen Andrews, executive director of the CT Health Policy Project, cast her first no vote as the panel's consumer representative. While she's happy that Merck is tackling CDI, she said she felt the sponsor needed to sort out whether the drug, which is intended to be given with standard-of-care antibiotics when a patient is first treated for an infection, could adversely affect the cure – a possibility the FDA raised in its presentation.

The lone abstention came from Amanda Corbett, a clinical associate professor and global pharmacology coordinator at the University of North Carolina's Institute for Global Health and Infectious Diseases. She said she had never abstained before, but her biggest challenge in voting was a lack of information.

Michael Green, a professor of pediatrics and surgery in the division of infectious diseases at the University of Pittsburgh School of Medicine, voted yes, but he said he feared that, if approved now, bezlotoxumab would be freely used by doctors who think more is better, which would increase the cost of treating CDI and perhaps harm some patients.

His colleague, Juan Gea-Banacloche, chief of the infectious diseases section at the National Cancer Institute, expressed similar thoughts. While recognizing the high cost of treating CDI, he said he couldn't help but wonder how much it would cost to prevent one case of CDI if bezlotoxumab were added to the initial treatment regimen for all patients.

Several panelists who voted yes encouraged the FDA to restrict the drug's use to patients who were most at risk of a recurrence and to warn about a potential for cardiovascular risks. A few questioned whether "recurrence" was the right word to use in labeling, as many patients would interpret that to mean "cured." A "sustained response" would be a better definition of what the drug appears to do, said Joan Hilton, an epidemiology and biostatistics professor in residence at the University of California, San Francisco School of Medicine.

MRSA Survivors Network founder and President Jeanine Thomas, the patient representative, was the only one on the panel who saw no way forward for the drug.

"We need superior therapies," she said. Bezlotoxumab is not significantly better than placebo, and further studies wouldn't make it better, she added.

STATISTICALLY SIGNIFICANT

According to the data presented at the meeting, bezlotoxumab demonstrated a 10 percent reduction in recurrence over placebo, a figure the FDA acknowledged as statistically significant. That translates into a 40 percent relative risk reduction, Merck officials said, noting that if the number held in real-world use, the drug could prevent nearly 50,000 incidents of CDI in the U.S. each year.

Panelist concerns reflected the dire need for new drugs in the space, the fragility of the patients, the societal and economic cost of CDI, and how little is known about the infectious disease. In its ongoing development of the antibody as a non-antibiotic approach to dealing with harmful bacteria, Merck is generating a wealth of data about CDI. If successful, the Kenilworth, N.J.-based drug company could help develop new strategies against drug-resistant bugs.

To date, the FDA has approved 50 monoclonal antibodies. If approved, bezlotoxumab would be only the second one to take on an infectious disease. Because the drug targets a toxin rather than the organism itself, there's been no evidence of the bug building a resistance to it, according to Merck.

The PDUFA date for the drug, which was granted priority review, is July 23. Merck licensed the drug in 2009 from Medarex, now part of Bristol-Myers Squibb Co. (See *BioWorld Today*, April 22, 2009.) //

OTHER NEWS TO NOTE

Addex Therapeutics SA, of Geneva, reported positive results with ADX71441, a GABAB receptor positive allosteric modulator, in a non-human primate model of cocaine self-administration. The results were obtained through an ongoing research collaboration with the U.S. National Institute of Drug Abuse. The effect of acute treatment with ADX71441 on intravenous (IV) cocaine self-administration was determined in rhesus monkeys that self-administered varying doses of cocaine (0.001-0.1 mg/kg/injection, IV). Specificity of the effect of ADX71441 was assessed by evaluating the response to food in sessions preceding and following the IV self-administration of cocaine phase of the experiments. In the initial dose-ranging studies, intra-muscular (IM) doses of ADX71441 (0.32-3.2 mg/kg) were administered 120 minutes before sessions in which 0.03 mg/kg cocaine was available for IV injection. The results indicate that ADX71441 dose-dependently decreased cocaine self-administration to approximately 10 percent of control values. The results further indicate that pretreatment with ADX71441 did not substantially effect food intake. In a second set of experiments, the effect of 1.0 or 3.2 mg/kg of ADX71441 on self-administration behavior was evaluated at a range of IV doses of cocaine and IV saline. Data show that ADX71441 decreased the self-administration of all doses of cocaine by 60-90 percent and had no effect on the IV self-administration of saline. In addition the effect was specific to cocaine.

BIO

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mounting pressure on the industry's blue chips to improve performance in the midst of a volatile stock market have placed heavy demands on partnering activity. In a super session on the final day of the BIO International Convention, a panel of veteran deal-makers debated whether big biopharmas will take a wait-and-see approach or throw caution to the wind and forge ahead with partnering and M&A.

Neel Patel, vice president of corporate development at Campbell Alliance, an Inventiv Health company, presented data from the 2016 Dealmakers' Intentions Study suggesting that deal-making volume will return to "historic norms" after hitting record levels in 2015. Given that return to normalcy, a key take-home was that buyers must exercise caution and not overpay for assets.

In the transition to a cooling environment, the study also suggested fewer partnerships and traditional licensing deals may occur in 2016, balanced by more outright and provisional acquisitions. Not surprisingly, in terms of expectations for deals by development stage, Patel predicted a higher proportion of sellers than buyers at preclinical and more buyers than sellers at phase III, with a relative balance between the parties at phase I and phase II.

Oncology assets, which have dominated deal-making in recent years, are facing more of a buyer's market as early innovators stake their claims across the landscape in immuno-oncology, providing a greater challenge for new entrants to break in. On the flip side, demand for antimicrobial agents has moved the infectious disease category to the opposite side of the deal spectrum, in what Patel called a "renaissance" for deal-making in the therapeutic category. Central nervous system assets also are expected to command high demand.

Some of the deal-making changes expected to occur this year aren't quite at the tipping point, according to panelists. Ellen Lubman, vice president of external science and innovation at Allergan plc, of Dublin, observed that "there's a still little bit of an overhang from loftiness of 2015" that continues to affect the views of privately held biopharmas on their valuations and up-front requirements.

With most small biopharmas still sitting on at least 12 to 18 months of cash, that sentiment may persist well into the second half of the year, according to Christian Hordo, head of business development at Juno Therapeutics Inc., in Seattle. But with the IPO window "less open" than before, these companies will face increasing pressure when they pursue follow-on financings. As reserves start to run drive, he expects to see an uptick in deals.

Henry Gosebruch, executive vice president and chief strategy officer at Abbvie Inc., of North Chicago, agreed, maintaining that a correction in the deal-making course sometimes requires up to a year.

"I expect the second half [of 2016] will get a little more active," he said.

Sellers should expect to encounter an altered universe of biopharmas, at once larger and more diverse than in the past – ranging from traditional pharma to regional and therapeutic specialists to large generics players – but also more focused on building leadership in specific therapeutic areas than taking all comers, as during the banner deal-making years. Consequently, partnering opportunities in a given indication may have only a handful of prospects rather than a dozen or more, as in days past. To clinch a deal, small companies will need to show how they can enhance a pipeline, add value to a particular program or accelerate an asset to market, panelists advised.

They also emphasized that deals aren't always about the money – not entirely, anyway. Thomas Zioncheck, global head of business development for neuroscience, ophthalmology, metabolic disease and research tools and technology at Genentech, a unit of Roche AG, of Basel, Switzerland, said the company is often approached by companies with plenty of cash that are seeking to partner "because they can take their programs only so far."

As to striking successful matches, Hordo advised the audience to "pick the right partner. Find a partner committed to your space. Take your time and be thoughtful up front."

Finally, panelists weighed in on the 2016 Presidential campaign and its impact on deal-making. Although hyperbole is, perhaps, unavoidable, Hordo acknowledged concern that the topic of drug pricing is swirling out of control in the political maelstrom. The result, he said, is that the message of the industry's life-saving agenda "is getting lost."

Although BIO and other industry organizations have developed educational campaigns about the impact of drug development on the improving patient care, "bottom up discussion also is important," Hordo maintained. "There's a role for everyone in the industry to step out and explain what we're doing. Stories are powerful. We all need to do a better job of being individual ambassadors." //

OTHER NEWS TO NOTE

Agenus Inc., of Lexington, Mass., said **Merck & Co. Inc.**, of Kenilworth, N.J., selected a lead product candidate under its license and research collaboration with Agenus. The antibody candidate selection together with several backup antibodies, discovered by Agenus, to an undisclosed Merck checkpoint target triggers a $2 million milestone payment from Merck.

Alkermes plc, of Dublin, said in a document filed with the SEC, that on June 3 the U.S. Patent and Trademark Office accepted two separate petitions for inter partes review (IPR) filed by **Luye Pharma Group Ltd.**, challenging U.S. Patent number 6,667,061, which is an Orange Book-listed patent for each of Bydureon, Risperdal Consta and Vivitrol. The company has three months to respond, following which the U.S. PTO has a further three-month period to decide whether or not to institute a review of the challenged claims of the '061 patent. It said it will oppose Luye's requests to institute the challenge of the '061 patent, and, if the U.S. PTO institutes such challenge, the company will oppose the full proceedings and vigorously defend the '061 patent.

Sorrento

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discovered by TNK Therapeutics Inc. (TNK), of San Diego. TNK, a cellular therapy company, is a subsidiary of Nasdaq-listed Sorrento Therapeutics Inc. (SRNE).

3SBio and TNK have formed a joint venture to develop the CAR T assets, not taking the more common cross-border licensing agreement route. 3SBio will have 51 percent ownership of the JV leaving TNK with a 49 percent stake.

The Chinese partner will put in $10 million investment to support the CAR T development program while TNK will provide the IP. The first candidate is aimed at carcinoembryonic antigen (CEA) positive cancers, which include colorectal, lung, liver and breast cancers.

"3SBio is in charge," Henry Ji, president and CEO of Sorrento, told *BioWorld Today*. "We simply transfer our knowledge, our technology and our compounds to 3SBio to be used in the regional market. They are in the driver's seat and are highly motivated."

Usually, joint ventures are much more relationship intensive than licensing. Licensing is often likened to dating, while joint ventures are more akin to marriage.

Not surprisingly, cultural clashes can make JVs short-term partnerships fraught with tension. But the JV between TNK and 3SBio has a good chance to be successful. TNK and Sorrento may appear to be American companies based in San Diego, but their founder, Henry Ji, is a China-born entrepreneur and scientist with strong ties to his homeland.

"I have known Jing Lou, the CEO, for a long time; he is a good friend," said Ji. "Our respect is based on scientific insights, and I admire his business operation very much. They are very innovative, and they want to do innovative therapy in the cancer space. CAR T is something the chairman has wanted to do – I believe – for a pretty long time. Our technology happens to be available and it is a good fit for them."

3SBio has a rich pipeline of over 20 class 1 candidates under development (class 1 is reserved for new drugs in China).

They also have several successful products on the market including TPIAO, the only commercialized recombinant human thrombopoietin (rhTPO) product in the world as well as EPIAO and SEPO, recombinant human erythropoietin (rhEPO) products. Another revenue generator for 3SBio has been Yisaipu, a first-to-market recombinant human tumor necrosis factor-a receptor II (TNFR) – IgG Fc fusion protein for the treatment of rheumatoid arthritis.

BETTER THAN A LICENSING DEAL

Setting up a China JV offers several advantages. It usually means greater profit sharing than a licensing deal, although patience is required given profitability can take a long time to be realized. Often there is no up-front licensing fee in JVs, saving resources for the development of the assets. This can work well for companies that are reluctant or unable to pay too much up front.

"Asian companies, typically, are not accustomed to paying out, they prefer profit sharing and risk sharing," said Ji. "The way to encourage them to work with you is to develop the product; otherwise they pay a big up-front and don't have enough money to do the development."

Greater scientific supervision is another advantage to JVs. According to Patrick Loofbourrow and Christina Zhang, partners at Cooley LLP Shanghai who recently gave a talk on JVs vs. licensing in China, JVs are good when "you want more control and visibility over the regulatory path – what will be happening in the trials and how they are constructed. There is little transparency into the operations of a license."

This was likely another consideration for Ji in making the deal, as he has global aspirations for the CAR T candidates being developed by the newly formed JV, and more than just profit sharing, he is looking for data sharing as well.

"In this deal, we share the data, too. It is a very good thing for us if we want to push the product in the North American, Japanese and European markets," said Ji.

He also highlighted that since Sorrento is a "discovery engine" with a vast library of antibodies, they need partners to help them get as many viable candidates as possible to the market. (See *BioWorld Today*, May 25, 2016.)

"It is critical for us to have a lot of companies to work with us on our compounds and with the compounds in clinical trials, to deploy our resources accordingly," explained Ji. "This way we will use our funds efficiently, and when we issue our proof-of-concept data, then we can move the program aggressively in other markets."

A little more than a month ago, Sorrento signed a JV deal with Yuhan Co. Ltd., of South Korea, creating Immuneoncia Therapeutics LLC and giving the Korean pharma its first R&D program. Sorrento handed over select global rights to an immune checkpoint antibody (keeping Japan, North America and Europe for itself) and global rights for two more unspecified immuno-oncology antibodies. Much like the 3SBio deal, Yuhan chipped in $10 million for development and has 51 percent ownership of the JV. (See *BioWorld Today*, April 8, 2016.)

But when the opportunity arises, Sorrento is also open to licensing deals. It signed a deal valued at $46 million with Lee's Pharmaceutical Holdings, of Hong Kong, for an anti-PD-L1 monoclonal antibody (MAb), STI-A1014, handing over Greater China rights. (See *BioWorld Today*, Oct. 8, 2014.)

In China, JVs can take some time to get government approval and to get up and running, but Ji expects the Chinese JV to be operational by August. Once approved, JVs can make up time as they are thought to be granted the same preferential treatment as local companies when making applications to the CFDA.

In China's CAR T space, they will face competition from

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Precision

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so are some of the leading companies operating here. The question at the moment is whether development of precision medicine in the country is a domestic or foreign affair? And where will the huge amount of government funding in the space go?

Of all the countries with precision medicine agendas, China has the largest, with planned investments of ¥60 billion (US$9.1 billion) aimed at making precision medicine a reality in the country. The government has a reputation of achieving its goals in a top-down fashion and with great impetus; this market is ready for a blossom in the near future.

In February 2015, President Xi Jinping announced the establishment of a precision medicine expert committee with 19 members, which marked the beginning of the country's precision medicine initiative.

One month later, the Ministry of Science and Technology (MOST) hosted the National Precision Medicine Strategic Experts Seminar where the government said it would pour ¥60 billion into precision medicine market development by 2030. About one-third of these funds will be from the central government while the rest would come from corporates and local governments.

In May 2015, the State Council released the Made in China 2025 plan encouraging domestic innovation and manufacturing to make China less dependent on imports in some areas. This plan mentioned the government would promote the development of novel targeted therapies such as CD22, CD147, T-cell therapy etc. Precision medicine will support this development.

MOST then included precision medicine as a National Key Research and Development Program and released guidelines on project application submission in March this year. Meanwhile, the 13th Five Year Plan listed genomics as one of the 1,000 major new technology programs to receive government support.

NARROWING THE SCOPE

Precision medicine is quite a broad term and can cover a range of applications. The 2016 National Key Research and Development Program set five major tasks for precision medicine research for the next five years:

- large-scale population-based cohort study;
- data integration, storage, usage and sharing platform;
- disease prevention, diagnosis and treatment research;
- R&D of clinical genomics technology;
- precision medicine execution framework.

Compared to the U.S.'s personalized medicine plan President Barack Obama launched last January, the Chinese precision medicine initiative has a much bigger scale, both in terms of funding and target population.

The central government of China plans to give out ¥20 billion (US$3 billion) to fund the initiatives on top of the ¥40 billion (US$6 billion) that will come from local governments and enterprises. The U.S., on the other hand, will set aside $215 million from its fiscal budget to develop personalized medicine, of which $138 million will go to the building of a new genetic biobank.

However, the allocation of the Chinese funding has yet to be disclosed.

"The government's funds will mostly go to research institutions and public hospitals, little will go directly into the industry," said Sun Hongye, chief technology officer and head of Wuxi Apptec's genomics subsidiary Wuxi Nextcode's China operations. "We're involved in many of the precision medicine research projects." (See *BioWorld Today*, May. 26, 2016.)

Many academic hospitals are establishing precision medicine centers. Shanghai Zhong Shan Hospital, the First Affiliated Hospital of Zhejiang, Beijing Tsinghua Chang Gung Hospital and the First Affiliated Hospital of Xi'an Jiao Tong University all established some sort of precision medical centers in 2015.

The industry sees a bright future for precision medicine in China, one that can be reflected in the new collaborations among Chinese companies, from established tech giants to start-up companies, with local and foreign partners.

Wuxi Apptec and Chinese telecommunication major Huawei inked a collaboration deal this March to build a national-level cloud platform for precision medicine. The cloud was launched at the end of May and is fully operational now.

In the same month, another Chinese pioneer genomics organization, Shenzhen-based BGI, and the University of Washington School of Medicine (UW Medicine) signed a memorandum of understanding to advance precision medicine for diagnosis, treatment and prevention of common and rare diseases together.

"The Huawei-Wuxi Apptec cloud platform is aimed at one of these four tasks, on data integration, storage, usage and sharing platform," said Helen Chen, Partner at L.E.K. Consulting. "The BGI-UW initiative is aimed at the large-scale population-based cohort study task."

IMPORTING TECHNOLOGY

However, the technologies involved in these deals are mostly foreign. Even Wuxi Apptec's genomics arm is of Icelandic origin.

"The technologies for precision medicine are mostly overseas, so the Chinese companies and participants more or less have to use international technology while the domestic ones are being developed," said Chen.

Wuxi Apptec bought Nextcode last year for $65 million and BGI acquired California-based genome sequencing company Complete Genomics in 2013 at $118 million.

So Chen raised a question: Are they Chinese or foreign?

Given genomics is a sensitive area, and the Chinese government is known for being very supportive and protective

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Allicense

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Sands' remarks came during a panel talk at Allicense 2016, held this year in conjunction with the 2016 BIO International Convention.

Nurix, of San Francisco, is working exclusively with Summit, N.J.-based Celgene in cancer, inflammation and immune disorders. Mutations in UPS genes are common drivers of many human cancers, and certain UPS genes function in normal physiology encoding key checkpoints in the immune response. The deal with Celgene built upon seed and series B investments by Third Rock Ventures and the Column Group that established the company. Sands previously co-founded and served as CEO of Lexicon Pharmaceuticals Inc., of The Woodlands, Texas. (See *BioWorld Today*, May 23, 2014, and Sept. 17, 2015.)

Getting the most from a platform technology is not simple, said Kent Hawryluk, chief business officer of La Jolla, Calif.-based Avidity Nanomedicines LLC. Former business officer of Marcadia Biotech Inc. until shortly after the obesity player was acquired by Basel, Switzerland-based Roche Holding Ltd., Hawryluk said it's "almost like there are two types of platform companies," one of which may inadvertently let its primary efforts lag. After "fishing around for a drug, you find a drug and say, 'Oh, great, now we're going,' and you kind of forget about the technology platform. Or maybe you don't [forget], but just by virtue of where your capital, and your peoples' focus and all goes, you atrophy, your platform sort of dies off." The platform model is becoming so popular that shoppers may decide on a "platform" that ultimately isn't one, he said. "I don't want to be critical of any company, and I don't have a particular one in mind, but I would just make the point that one successful SAR [structure-activity relationship] does not make a platform," he said. "Is it extensible, is it reproducible, is it really allowing you to do something clearly unique? But [even] if you have that, I think, it really is a struggle." (See *BioWorld Today*, Jan. 3, 2011.)

With Avidity, via partnerships, Hawryluk is engineering a new class of precision medicines – antibody-small interfering RNA (siRNA) conjugates that pair the strengths of monoclonal antibodies with siRNA-based therapeutics. The firm decided that it would "internally differentiate to enable others' pipelines," he said.

"There are reasons for that, maybe unique to our company," which needed antibodies that could be provided by collaborators, so "it made sense to swim downstream" and tap existing programs for deals that could exploit Avidity's platform. The strategy "leads to [the question of], how do you partner your technology platform to preserve your rights and ability to do additional partnerships?" he said. "That's always going to be the push and pull. Because pharma now has more sophistication and experience in dealing with these platform-oriented partnerships, they're a little more forgiving or even generous, [yet] limited in terms of what they will look for." The sharper focus makes for cleaner, stronger deals.

"This is going to be a new paradigm in business development" that involves how agreements are put together when a platform is involved, he said, and one question will be asked with particular specificity: "What is it that you're partnering?" Lebanon, N.H.-based Adimab LLC's antibody discovery and optimization technology has 140 different programs ongoing, he said – "an extreme case" of successfully going wide.

SMALL MOLECULES LAG

Christopher Denn, a partner in Goodwin Procter's life sciences practice, said lawyers have grown savvy about designing the arrangements between platform companies and their suitors in order to strike "a sensible balance of risk between your current deal and your next deal."

As a platform owner, "it's difficult, when you're negotiating, to tell a big pharma company who's going to hand you a big check that we can't give you the right to enforce the platform patents" or that the pharma firm may enforce related patents selectively, he said. But the move is necessary for other users to come aboard via later deals.

Sands, of Nurix, said that a prolific platform is one key to staying pure and undistracted. With one, "you can operate with a horizontal business model and probably do some fantastically broad deals and stay away from the clinical development [and] commercialization shifting of gears," but "If the platform doesn't have litters of eight and 10 pups coming out of it, then you really do have to participate" in those other realms, he said.

"Early and often," was the general consensus about partnering platforms. But, asked whether an improvement in the science is powering the field or simply more availability of outside resources, panelists were not so harmonic.

Richard Soll, senior vice president of international discovery service with Shanghai-based Wuxi Apptec, made the case for medicinal chemistry's advance, pointing out that his firm lists 4,000 staffers in that department.

Sands, however, said "some things have accelerated but others just haven't. To be honest, one of the areas that has not accelerated is medicinal chemistry. You said you have 4,000 chemists. That's not a technology, that's an army. A lot of small companies can't muster that." Small-molecule research has lagged, he said.

"Sure, X-ray crystal structures are better now, seem to work better. OK, [but] it's still that bump and grind of making new molecules by hand, basically. Whereas other areas like genomics sequencing and antibody technology have really accelerated. They can do a lot more a lot quicker."

The small-molecule space, by contrast, is "very similar to what it was 20 years ago, unfortunately," he said. //

Arthritis

Continued from page 1

the development of new treatments for rheumatoid arthritis (RA).

RA is a chronic autoimmune disease affecting the body's joints. The immune responses responsible for the pathogenesis of RA, namely the Type 1 (Th1) and Type 17 (Th17) responses, originally evolved to combat infections by viruses and bacteria. In patients with RA, these immune responses also attack the cartilage in the joints, leading to long-term tissue damage, inflammation and pain.

However, little is known about how these immune responses counteract the characteristic chronic inflammation associated with RA, and the link between parasitic worm infestations and the disease discovered by the new study was previously unknown.

In the June 7, 2016, edition of *Nature Communications*, researchers led by Aline Bozec, a professor with the University Clinic Erlangen and Friedrich Alexander University of Erlangen Nuremberg, reported having induced RA in mice and infected a subset of animals with the parasitic worm *Nippostrongylus brasiliensis*, in order to study their immune responses.

The research project into the effect of parasitic worms on the immune system was initiated by Zhu Chen, who is now a clinical immunologist in the Department of Rheumatology and Immunology at Anhui Medical University Affiliated Provincial Hospital in Heifei, China.

A gastrointestinal nematode, *N. brasiliensis* is a well-studied roundworm due to its relatively simple life-cycle and its ability to be used in animal models of the immune response to such parasites and the development of protective immunity against them.

In several separate experiments, Bozec and her colleagues compared mice infected with *N. brasiliensis* with controls and discovered that the worm infections protected the mice against RA and that this protection was mediated by a TH2 immune response activated by infection with *N. brasiliensis*.

"In two independent models of RA, we demonstrated that infection with *N. brasiliensis* led to a Th2 response and eosinophil accumulation in the joints, which was associated with robust inhibition of arthritis and protection from bone loss," Bozec told *BioWorld Today*. "Mechanistically, this protective effect is dependent on interleukin (IL)-4/IL-13-induced STAT6 activation in hematopoietic cells."

She explained that STAT6 is a member of the signal transducer and activator of transcription family of proteins, which are key intracellular transcription factors that mediate various aspects of cellular differentiation, proliferation and immunity, including the inflammatory response.

Worm infection also led to a markedly increased number of eosinophils, types of white blood cells that are responsible for combating such multicellular parasites. "Hypereosinophilia triggered by *N. brasiliensis* infection also contributes to the resolution of arthritis by stimulating a shift from pro-inflammatory into anti-inflammatory macrophages in the joints," said Bozec.

Specifically, the researchers demonstrated that the Th2 response was responsible for expelling the worms from the mice and that it promoted tissue repair and prevented inflammation, thereby effectively counteracting the Th1 and Th17 responses underlying RA.

"We didn't show directly the role of Th2 responses in expelling the worm from the host, because *N. brasiliensis* infection is already a well-established model to induce and examine Th2 immune responses in rodents," said Bozec.

However, "it [*N. brasiliensis* infection] is known to trigger the production of Th2 anti-inflammatory cytokines such as IL-4 and IL-13, which is accompanied by the activation and proliferation of CD4+Th2 cells, eosinophilia, and goblet and mucosal mast cell hyperplasia," she added

"In our experimental design we induced arthritis in the mice 6 days after *N. brasiliensis* infection, when the worm was almost expelled from the host. Nine days after, we analyzed the frequency of Th1, Th2 and Th17 cells in the spleen and showed that only Th2 cells increased significantly after infection.

"The initiation of arthritis leads to a significant increase of the Th2 cytokines IL-4, IL-5 and IL-13 producing cells in the spleen and mesenteric lymph nodes and an accumulation of eosinophils in the joints of *N. brasiliensis* infected mice compared to uninfected controls," she explained.

"The Th2 response was accompanied by a reduced frequency of neutrophils as well as a shift from pro- into anti-inflammatory macrophages in the joints, leading to reduced inflammation and attenuation of arthritis in mice infected with worms compared to uninfected mice."

These are unprecedented and highly significant findings, since "our group was the first to have unravelled the molecular mechanisms behind the Th2 immune responses, which might play a protective role in RA," Bozec told *BioWorld Today*.

In addition, they found that the cellular components of the Th2 responses were present in samples of synovial fluid taken from the knees of 20 RA patients, suggesting these responses are engaged in suppression of the pathophysiology of RA, even in the absence of worm infection.

"We demonstrated the presence of GATA3-positive cells in the synovial tissue of RA patients," she said, explaining that GATA3 is another transcription factor important for the differentiation of Th2 cells. "We also detected the expression of eosinophil peroxidase, which is a marker for eosinophils."

These study findings strongly suggest that activation of the Th2 immune response with the use of such vaccine-like stimuli could pave the way for the future development of new treatments for RA in humans.

"By detecting cellular components of the Th2-eosinophil response in RA patients, we could clearly demonstrate that

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Arthritis

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the described pathway also plays a role in human disease," said Bozec. "A shift from Th1- or Th17- to a Th2-like response by treatment with Th2-promoting cytokines like IL-4 or IL-13, or with non-infectious worm-derived antigens, could trigger a Th2 response," she speculated.

Meanwhile, Bozec's research team's next step and ultimate objective will be "to determine whether it is possible to define an immune signature for resolution in patients with rheumatoid arthritis." //

Precision

Continued from page 6

of domestic enterprises, many expected that the targeted $9.1 billion funding would go to the domestic industry. But the inclusion of foreign companies in the new precision medicine key R&D projects proves that the government wants the best, be it foreign or local.

"I was really pleased to see that precision medicine research funding announced as part of the National Key Research and Development Program specifically called out no limitations on whether the applicant is Chinese or foreign," said Chen from L.E.K. "The applicant has to be registered in China, however, and have to have the ability to get funding from local governments as there are expectations of local matching funding for these projects." //

Sorrento

Continued from page 5

Innovative Cellular Therapeutics Inc. (ICT), of Shanghai. ICT has commenced a multicenter phase 1 trial for leukemia to study self-discovered SDS-19CAR. And heavyweight Juno Therapeutics Inc. has set up a JV of its own with Wuxi Apptec (See *BioWorld Today*, April 13, 2016, and May 25, 2016.) //

OTHER NEWS TO NOTE

Astrazeneca plc, of London, said it has entered a commercialization agreement with Aspen Global Inc. (AGI), part of the Aspen Group, for rights to its global anesthetics portfolio outside the U.S. The agreement covers seven established medicines - Diprivan (general anesthesia), EMLA (topical anesthetic) and five local anesthetics (Xylocaine/Xylocard/Xyloproct, Marcaine, Naropin, Carbocaine and Citanest). AGI will pay $520 million up front and up to $250 million in a product sales-related payment, as well as double-digit percentage trademark royalties on product sales. Astrazeneca will manufacture and supply the products on a cost plus basis to AGI for an initial period of 10 years. Upon completion, Aspen will assume responsibility for all activities relating to the sale of the portfolio in all relevant markets.

Batavia Biosciences BV, of Leiden, the Netherlands, said it received a $3.8 million grant from the Bill & Melinda Gates Foundation to fund work focused on increasing vaccine availability and affordability in the developing world. Efforts are aimed at reducing manufacturing costs of vaccines for polio and rotavirus by collaborating by **Proventus Bio Inc.**, of Atlanta, to use its RNA screening technology with Batavia's gene-editing platform and cell line expertise to generate a range of new cell substrates to increase production yield and enhance vaccine availability against reduced costs.

Bioaegis Therapeutics Inc., of Boston, said the National Institute of Allergy and Infectious Disease awarded a three-year, $2.8 million grant to a partnership between the company and Harvard School of Public Health researchers to advance the study of plasma gelsolin (pGSN) replacement as a therapy for antibiotic-resistant pneumonia. pGSN becomes depleted in a wide range of inflammatory conditions, and critically low levels associate with significant morbidity and mortality.

Cellceutix Corp., of Beverly, Mass., said the U.S. District Court for the Southern District of New York granted the company's motion to dismiss a securities class action lawsuit brought against the firm by a plaintiff represented by the Rosen Law Firm. Cellceutix said an anonymous "libelous" article published by Seeking Alpha prompted the filing.

Clinigen Group plc, of Burton on Trent, U.K., and **Basilea Pharmaceutica NV**, of Basel, Switzerland, said they initiated a managed access program for isavuconazole to treat patients with invasive fungal infections in those European countries where isavuconazole has been approved but is not yet commercially available. Isavuconazole is an intravenous and oral triazole antifungal indicated for the treatment of adult patients with invasive aspergillosis and adult patients with mucormycosis for whom amphotericin B is inappropriate. It gained FDA and EMA approval last year.

Galapagos NV, of Mechelen, Belgium, said Euronext selected the firm for inclusion in the AEX1 Index on Euronext in Amsterdam, effective June 20. It's the first biotech to be included in the index.

Innovative Targeting Solutions Inc. (ITS), of San Francisco, said it inked a research collaboration with **Merck & Co. Inc.**, of Kenilworth, N.J., which will use its Hutarg research platform to identify and develop biologic therapeutic candidates directed toward targets that have historically been a challenge for biologics. Under the terms of the agreement, ITS will be eligible for payments associated with the achievement of specified milestones as well as tiered royalty payments on sales of any products. The total potential value of this agreement is about $150 million. Further details of the agreement were not disclosed.

OTHER NEWS TO NOTE

Insmed Inc., of Bridgewater, N.J., said it withdrew its marketing authorization application from the EMA for Arikayce (liposomal amikacin for inhalation) for the treatment of nontuberculous mycobacteria lung disease. The filing was based on data from the company's phase II study, which, according to a May opinion by the agency's Committee for Medicinal Products for Human Use, was not sufficient to support approval. Insmed said it intends to resubmit the application when data from the global phase III trial are available.

Ironwood Pharmaceuticals Inc., of Cambridge, Mass., and **Allergan plc**, of Dublin, said the FDA accepted for review the supplemental new drug application for the 72-mcg dose of linaclotide for use in the treatment of adults with chronic idiopathic constipation (CIC). The application was based on data from a phase III trial in 1,223 adults testing the guanylate cyclase C agonist. A PDUFA date is expected in early 2017. Linaclotide, branded Linzess, is currently approved by the FDA for the treatment of adults with CIC as a 145-mcg capsule to be taken once per day and as a 2,900-mcg capsule for treating irritable bowel syndrome with constipation.

Joslin Diabetes Center, of Boston, announced a newly signed collaboration with **Sanofi SA**, of Paris, which extends their ongoing collaboration to explore targets for treatment of diabetes. The parties will direct joint efforts on research and development of new therapeutic options for the treatment of diabetic nephropathy, and explore implications of diabetes on cardiovascular disease.

Kempharm Inc., of Coralville, Iowa, said it filed an amendment request with the FDA in regard to its new drug application (NDA) for Apadaz (benzhydrocodone hydrochloride and acetaminophen), an abuse-deterrent drug candidate to manage acute pain in the short term. The company is seeking to include additional information in the agency's review of the NDA for Apadaz. The FDA had set a target action date of June 9.

Lion Biotechnologies Inc., of New York, said its board of directors will reschedule its annual stockholders meeting that was set for June 10. Two new members were recently appointed with a third appointment due shortly. A new meeting is required to allow those new directors to stand for election and to present a number of proposals to stockholders. The new time and date have not yet been set.

Lpath Inc., of San Diego, said a 14 to 1 reverse stock split will be implemented 5 p.m. ET Friday. That action will take the company's shares from about 33.1 million down to 2.36 million. The split is needed for Lpath to meet Nasdaq trading requirements. The stock will continue to trade under its current symbol (NASDAQ:LPTN).

Menarini Asia-Pacific Holdings Pte Ltd., of Singapore, part of the Menarini Group, and MSD, also known as **Merck & Co. Inc.**, Kenilworth, N.J., said they entered a multiyear agreement for Menarini Asia-Pacific to take responsibility for sales, marketing and distribution of a number of MSD's pharma brands in Asia-Pacific, effective January 2016. The agreement covers Malaysia, Singapore, Philippines, Hong Kong, Brunei and Macao, with annual sales of more than $70 million, and the brands focus on a variety of areas, including cardiology, respiratory, women's health, central nervous system and dermatology. The two companies have similar agreements in Europe.

Pnuvax Inc., of Chalfont St. Giles, UK, and GE Healthcare's Life Sciences business, of Kingston, Ontario, Canada, entered an agreement under which Pnuvax can acquire GE Healthcare's intellectual property relating to an inactivated yellow fever vaccine. Pnuvax will purchase a GE Healthcare Life Sciences Flexfactory biomanufacturing platform and the two companies plan a collaboration to optimize the manufacturing process for the new vaccine. Financial terms were not disclosed.

Puricore plc, of Malvern, Pa., said that a pre-investigational new drug application (IND) meeting with the FDA, it is confident that the company's IND for lead candidate PR022, for atopic dermatitis, will be filed on schedule by the first quarter of 2017 and that its clinical trial plan would be "straightforward."

Coming Monday in *BioWorld Insight*

RESEARCH ADVANCES OUR UNDERSTANDING OF MITOCHONDRIAL DISEASE

SAN FRANCISCO – Advances in genomics are expanding our knowledge of diseases associated with mitochondrial DNA mutations. Understanding mitochondrial diseases is a significant challenge because of the diversity of human disorders that result, noted Michio Hirano, chief, Neuromuscular Division at Columbia University Medical Center, who was moderating a panel at the BIO 2016 International Convention on understanding mitochondria and mitochondrial disease. The panel was one of three devoted to the disease and *BioWorld Insight* reports on these sessions and also examines the clinical pipeline of products targeting mitochondrial disease.

NEW CLINICAL TRIAL DESIGNS: ANATOMY IS NOT DESTINY, BUT DRIVERS AREN'T EITHER

CHICAGO – Attendees are accustomed to hearing results from phase III trials of investigational agents at the annual meeting of the American Society of Clinical Oncology. And at the meeting, which ran from June 3-7 in Chicago, there were some of those presentations. But the denizens of McCormick Place found themselves contending with somewhat atypical fare this year, with less than the usual buzz around such trials. That change is partly a lull. But it is partly a consequence, and a reflection, of the fact that clinical trials are changing.

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OTHER NEWS TO NOTE

Synta Pharmaceuticals Corp., of Lexington, Mass., said that a shareholder vote regarding its proposed merger with **Madrigal Pharmaceuticals Inc.** will be held July 21 in Boston. The combined company will focus on the development of novel small-molecule drugs addressing major unmet needs in cardiovascular-metabolic diseases and non-alcoholic steatohepatitis. (See *BioWorld Today*, April 15, 2016.)

Targovax AS, of Oslo, Norway, gained regulatory approval to conduct a study in Spain to assess ONCOS-102 in combination with chemotherapy in patients with malignant pleural mesothelioma, a rare type of cancer in the lining of the lung. The randomized phase I/II trial will include 30 patients, with a phase Ib safety lead-in cohort of six patients. Its main objectives are determination of safety, immune activation at lesional level and in peripheral blood, clinical response and the correlation between clinical outcome and the immunological activation. It will be the first test of the virus-based immunotherapy platform in combination with chemotherapy.

Theratechnologies Inc., of Montreal, said that the government of Quebec, the province where Egrifta (tesamorelin) was discovered, has refused to add it to the list of reimbursed medications. According to the company, the decision by the Quebec Minister of Health, Gaétan Barrette, is based on a recommendation by the Institut national d'excellence en santé et services sociaux, which concluded that the decrease of visceral adipose tissue in HIV patients does not constitute a therapeutic advantage. Theratechnologies president and CEO Luc Tanguay said that it was "paradoxical that, after supporting the development of Egrifta through tax credits, the government will not accept to reimburse it."

IN THE CLINIC

Acura Pharmaceuticals Inc., of Palatine, Ill., said that during a pharmacokinetic study in healthy adults, LTX-04P, a hydromorphone hydrochloride immediate-release tablet, successfully retarded the release of the active opioid ingredient when four, six and eight intact tablets were ingested. The data came from the second cohort of study 400.

Agios Pharmaceuticals Inc., of Cambridge, Mass., said that during a phase I healthy volunteers study, dosing of the company's experimental therapy for pyruvate kinase (PK) deficiency, PAG-519, resulted in a dose-dependent increase in pyruvate kinase-R activity as evidenced by a substantial increase in adenosine triphosphate and decrease in 2,3-DPG (2,3-diphosphoglycerate) levels, which are important biomarkers of PKR activation in healthy volunteers. The company said that the data support the hypothesis that AG-519 enhances PKR activity and has the potential to correct the underlying defect of pyruvate kinase deficiency, a rare, potentially debilitating, congenital anemia. While there were no significant adverse events reported during the study, one case of grade 2 thrombocytopenia in a participant receiving AG-519 at the 375 mg dose in one part of the trial appeared to spook some investors, sending Agios shares (NASDAQ:AGIO) down 15 percent to close at $56.22 on Thursday.

Alder Biopharmaceuticals Inc., of Bothell, Wash., said data from phase IIb and phase I trials of ALD403 to prevent migraine and preclinical data from a case study of ALD403 and other calcitonin gene-related peptide (CGRP) antibodies were presented at the 58th annual scientific meeting of the American Headache Society in San Diego. The randomized, double-blind, placebo-controlled phase II trial of ALD403 showed that a single intravenous (IV) dose of 100 mg or 300 mg met the primary efficacy endpoint, producing a 75 percent reduction in migraine days over 12 weeks in 33 percent and 31 percent of patients, respectively ($p < 0.05$). A single administration of ALD403 also resulted in an immediate and durable mean reduction in migraine days from baseline throughout the 12 weeks, meeting the secondary efficacy endpoint. The safety profile was consistent with earlier ALD403 trials; no drug-related safety signals were identified. Phase I pharmacokinetic and pharmacodynamic results supported additional evaluation in later-stage trials of ALD403, with intramuscular injections resulting in higher absolute bioavailability, compared to subcutaneous dosing. The preclinical data comparing the binding kinetics of ALD403 to two other anti-CGRP monoclonal antibodies showed that ALD403 bound to CGRP differently, showing high affinity and rapid target engagement.

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., initiated a phase I trial of ALN-TTRsc02, its subcutaneously administered RNAi candidate to treat transthyretin (TTR)-mediated amyloidosis, or ATTR amyloidosis. The randomized, placebo-controlled, single ascending-dose study is expected to enroll up to 100 healthy volunteers to evaluate safety and tolerability of a single subcutaneous dose of ALN-TTRsc02. Secondary objectives include evaluation of pharmacokinetics and clinical activity, as measured by knockdown of serum TTR levels, and identification of the appropriate dose and regimen for a pivotal study. The company expects to report initial data from the study in late 2016 and, if positive, to initiate a phase III study next year.

IN THE CLINIC

Amgen Inc., of Thousand Oaks, Calif., reported top-line findings from its global phase II study evaluating the efficacy and safety of erenumab (AMG 334) to prevent chronic migraine. The study met its primary endpoint of change in monthly migraine days, with a statistically significant reduction in migraine days for both the 70 mg and 140 mg doses. At baseline, patients enrolled in the study were experiencing approximately 18 migraine days per month. They were randomized to placebo or one of the two erenumab doses subcutaneously, once monthly. Patients experienced a 6.6-day reduction from baseline in monthly migraine days in each of the erenumab treatment arms compared to a 4.2-day reduction in the placebo arm. The safety profile of erenumab was similar to placebo across both treatment arms. No adverse events (AE) were reported in greater than 5 percent of patients treated with erenumab; the most common AEs were injection site pain, upper respiratory tract infection and nausea. Amgen said is continuing to analyze the data, which will be submitted for presentation at an undisclosed medical meeting and for publication. The company expects to report phase III episodic migraine data for erenumab later in 2016.

Arrowhead Pharmaceuticals Inc., of Pasadena, Calif., initiated a phase I/II safety, tolerability and pharmacokinetics study of ARC-521, its second RNAi-based candidate, designed to treat chronic hepatitis B virus (HBV) infection. The placebo-controlled, double-blind, dose escalation study of ARC-521 in healthy volunteers includes a sequential, multiple-dose, open-label part in patients with chronic HBV. Healthy volunteers will enroll sequentially into six escalating dose levels, with six subjects per dose level, randomized to a single dose of ARC-521 or placebo. Chronic HBV patients who are negative for Hepatitis B e-antigen (HBeAg) at screening will enroll sequentially into three dose levels, with eight patients per dose level, to three monthly doses of open-label ARC-521. The study is recruiting at a single center in New Zealand. Arrowhead plans to add additional centers in other countries, pending regulatory and ethics reviews. The study may include have multiple readouts, including single-dose safety data, single-dose antiviral activity data and multiple-dose safety and antiviral activity data.

Avanir Pharmaceuticals Inc., of Aliso Viejo, Calif., said complete results from the PRISM II study of Nuedexta (dextromethorphan hydrobromide/quinidine sulfate), which showed improvement of pseudobulbar affect (PBA) following treatment in patients with Alzheimer's disease and other dementias, stroke and traumatic brain injury, were published online in *BMC Neurology.* The study, which included 367 participants who received Nuedexta for 90 days, showed the Center for Neurologic Study–Lability Scale (CNS-LS) score improved from a mean of 20.5 at baseline to 12.8 ($P<0.001$) at the 90-day endpoint, consistent with results seen in the phase III trial of Nuedexta. PBA episodes were reduced by 72.6 percent ($P<0.001$) compared to baseline at the 90-day endpoint. The adverse event (AE) profile in PRISM II was consistent with the known safety profile of Nuedexta, with diarrhea (5.4 percent), headache (4.1 percent), urinary tract infection (2.7 percent) and dizziness (2.5 percent) as the most common AEs. (See *BioWorld Today*, Dec. 3, 2014.)

Basilea Pharmaceutica Ltd., of Basel, Switzerland, said final data from the first-in-human phase I/IIa study of the intravenous (I.V.) form of its tumor checkpoint controller, BAL101553, were presented at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago. In the open-label phase I/IIa study, I.V. BAL101553 was administered over two hours on days 1, 8 and 15 of 28-day treatment cycles to patients with advanced solid tumors who failed standard therapy or for whom no effective standard therapy was available. Patients with colorectal cancer, non-small-cell lung cancer, pancreatic, ovarian, gastric and triple negative breast cancer were included in the phase IIa portion of the study. Of 59 patients evaluable for efficacy, 39 received 30 mg/m2 as the starting or adjusted dose. Of these, one long-lasting partial response of more than two years and one prolonged stable disease of six months were observed in two patients with ampullary (pancreaticobiliary) cancers. Nine additional patients presented stable disease of two to eight months. Overall, the drug was well tolerated in the 15-30 mg/m2 dose groups, where patients were on treatment longer and showed more signals of clinical activity than patients treated at higher doses of 45-80 mg/m2. The recommended phase II dose for BAL101553 was therefore determined to be 30 mg/m2. Dose-limiting adverse effects (AE) included transient and reversible grade 2 to grade 3 gait disturbance, which occurred with transient grade 1 to grade 2 peripheral sensory neuropathy, and asymptomatic and reversible myocardial ischemia. The AEs appeared primarily related to the peak drug plasma concentration.

Bioblast Pharma Ltd., of New Haven, Conn., said it plans to initiate a phase IIb trial with trehalose intravenous (I.V.) solution in oculopharyngeal muscular dystrophy during the second half of 2016 and initiated a scientific and business assessment to determine the suitability of using the therapy in other orphan diseases. The company plans to enroll more than 70 patients in the double-blind, placebo-controlled phase IIb trial at up to 15 sites in the U.S. and Canada.

Cerulean Pharma Inc., of Waltham, Mass., said the manuscript of clinical data for its lead compound, CRLX101, was published in *Annals of Oncology*, highlighting from an open-label, single arm phase Ib/II investigator-sponsored trial of CRLX101 in combination with Avastin (bevacizumab, Roche AG) in patients with metastatic renal cell carcinoma. The trial achieved its primary endpoint of establishing a recommended phase II dose and showed preliminary anti-tumor activity. Results from the trial also were presented at the 2015 American Society of Clinical Oncology annual meeting on June 1, 2015, and at the 2015 International Kidney Cancer Symposium on Nov. 4, 2015. The compound is a nanoparticle-drug conjugate designed to concentrate in tumors and slowly release its anti-cancer payload, camptothecin, inside tumor cells. CRLX101 inhibits topoisomerase 1, which is involved in cellular replication, and hypoxia-inducible factor-1α.

IN THE CLINIC

Cidara Therapeutics Inc., of San Diego, dosed the first patient in Radiant, a phase II trial comparing the safety and tolerability of echinocandin-class antifungal, or CD101, to standard-of-care fluconazole for the treatment of acute vulvovaginal candidiasis. Radiant will evaluate two topical formulations of CD101.

Eli Lilly and Co., of Indianapolis, and **Incyte Corp.**, of Wilmington, Del., said that in two phase III trials patients with rheumatoid arthritis (RA) treated with baricitinib reported significant improvements in quality of life symptoms and other patient-reported outcomes compared to methotrexate or Humira (adalimumab, Abbvie Inc.) Patients with RA also reported improvement in productivity at work. In these studies, significant improvements in patient-reported measures, including pain, physical function, tiredness and morning joint stiffness, were observed as early as one week after initial treatment with baricitinib, the company said. The findings were presented at the Annual European Congress of Rheumatology in London. In the RA-Begin trial, at 24 weeks, 81 percent of patients receiving baricitinib monotherapy and 79 percent of patients receiving baricitinib plus methotrexate had clinically meaningful improvement in physical function compared with 70 percent among those receiving methotrexate alone ($p < 0.05$). In the RA-Beam trial, where all patients received background methotrexate therapy, at 52 weeks, 68 percent of patients treated with baricitinib reported clinically meaningful improvement in physical function compared with 58 percent of patients on Humira ($p < 0.01$). At 52 weeks, baricitinib was also associated with significant improvement in pain, and clinically meaningful improvement in fatigue and the physical health components of quality of life compared with Humira. Baricitinib is a once-daily oral highly selective JAK1 and JAK2 inhibitor. Separately, Lilly said that *The New England Journal of Medicine* has published detailed results from three pivotal phase III studies – Uncover-1, Uncover-2 and Uncover-3 – that demonstrated the efficacy and safety of Taltz (ixekizumab) through 60 weeks in patients with moderate-to-severe plaque psoriasis. This publication also detailed 12-week efficacy data for patients treated with Taltz in Uncover-1. The drug is a humanized IgG4 monoclonal antibody that selectively binds with interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Taltz inhibits the release of pro-inflammatory cytokines and chemokines. Taltz was approved by the FDA in March 2016 for the treatment of moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Fibrogen Inc., of San Francisco, said it will receive a $10 million milestone payment from **Astellas Pharma Inc.**, of Tokyo, by July 2016, triggered by the initiation by Astellas of the first phase III clinical study in Japan of roxadustat (ASP1517 or FG-4592) for treatment of anemia associated with chronic kidney disease in patients on dialysis. Roxadustat, an orally administered small molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase, is the most clinically advanced candidate in this new class of potential anemia therapeutic agents, the company said. (See *BioWorld Today*, May 1, 2006.)

Galderma SA, of Lausanne, Switzerland, said its trifarotene development program targeting lamellar ichthyosis, a debilitating orphan disease resulting in the formation of scales covering the skin, was demonstrated to be safe and well-tolerated in a phase I study. Trifarotene is new retinoic acid receptor (RAR) agonist specifically designed for high selectivity to its target (RARγ) and low systemic metabolic stability, the company said.

Genocea Biosciences Inc., of Cambridge, Mass., said it will present updated data on the company's investigational immunotherapies at the American Society for Microbiology annual general meeting, ASM Microbe 2016, later this month in Boston. Data from the phase II dose-optimization trial evaluating GEN-003 for the treatment of genital herpes will be highlighted, showing statistically significant reductions in viral shedding and sustained efficacy 12 months after completion of dosing. Trends seen in reducing nasopharyngeal colonization in the phase IIa trial with GEN-004 for pneumococcal disease demonstrates the potential of the vaccine's concept, which the company said it hopes will lead to a partnership to advance the program.

Kineta Inc., of Seattle, released new, positive dalazatide data at the American College of Rheumatology's Annual Meeting from its recent phase Ib active plaque psoriasis clinical trial which showed validated blood biomarkers that confirm the drug's mechanism of action for psoriasis. Kineta and its collaborators identified a unique set of cell population markers and cytokines from psoriasis patients that confirm both drug activity and clinical response to dalazatide treatment.

Momenta Pharmaceuticals Inc., of Cambridge, Mass., dosed the first healthy volunteers in a phase I randomized, double-blind, placebo-controlled, ascending-dose cohort study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of M281, an anti-FcRn monoclonal antibody, for the treatment of autoimmune diseases. In preclinical models, M281 potently antagonizes FcRn binding of IgGs and rapidly diminishes circulating levels of IgG antibodies, the primary pathogenic agent in a number of autoimmune diseases. The study will enroll up to approximately 72 healthy volunteers.

Otonomy Inc., of San Diego, enrolled the first patient in the single OTIPRIO phase III clinical trial in pediatric and adult patients with acute otitis externa, also known as swimmer's ear. The company expects to complete this trial and report topline results in the fourth quarter of 2016. The one-month, prospective, randomized, double-blind, sham-controlled, multicenter, phase III clinical trial is expected to enroll approximately 500 patients age 6 months and older with acute otitis externa. The primary endpoint is clinical cure at day eight defined as complete resolution of the signs and symptoms related to acute otitis externa as determined by a blinded clinical assessor.

IN THE CLINIC

Paradigm Biopharmaceuticals Ltd., of Melbourne, Australia, said pentosan polysulfate sodium (PPS) will be delivered intranasally for the first time in human volunteers in a phase I trial assessing the candidate in hay fever. Recruitment for a phase II trial investigating the use of PPS in treating bone marrow lesions arising from acute injury, such as ruptured anterior cruciate ligaments, is ongoing. Interim analysis is planned for December 2016.

Prothena Corp., of Dublin, reported clinical results from a phase I double-blind, placebo-controlled, single ascending dose study of PRX003 in healthy volunteers. PRX003 is a monoclonal antibody targeting melanoma cell adhesion molecule (MCAM), believed to be an integral mediator of Th17 cell pathogenesis, for the potential treatment of inflammatory diseases where multiple cytokines play a role. PRX003 was safe and well-tolerated following a single infusion, up to and including the highest dose level tested of 30 mg/kg. Further, results from this study showed that administration of PRX003 led to greater than 95 percent neutralization of MCAM at saturating drug exposures. The data also showed a statistically significant ($p<0.0001$) dose-dependent duration of downregulation of MCAM on Th17 cells.

Sandoz Inc., a division of Basel, Switzerland-based Novartis AG, reported results from two key studies comparing its biosimilar etanercept and rituximab candidates with the originator products Enbrel and Mabthera, respectively. In both studies, the primary endpoints of achieving PK bioequivalence were met. The studies were presented at the Annual European Congress of Rheumatology. Etanercept and rituximab are indicated to treat autoimmune diseases such as rheumatoid arthritis. The phase I etanercept trial demonstrated PK bioequivalence and no clinically meaningful differences in safety, tolerability and immunogenicity between the biosimilar candidate and the etanercept originator product. The phase II rituximab trial demonstrated PK bioequivalence and similar PD, safety, efficacy and immunogenicity between the biosimilar candidate and the rituximab originator product.

Samsung Bioepis Co. Ltd., the joint venture between **Samsung Biologics Co. Ltd.**, of Seoul, South Korea, and **Biogen Inc.**, of Cambridge, Mass., presented data at the Annual European Congress of Rheumatology in London showing the comparable long-term efficacy, safety and immunogenicity of Benepali (etanercept) and Flixabi (infliximab). No treatment-emergent safety or immunogenicity issues occurred in patients who were switched from the reference product, Enbrel (etanercept, Amgen Inc.) to Benepali, and efficacy was sustained for up to two years. Comparable safety, immunogenicity and sustained efficacy also were shown in patients switched from Remicade (infliximab, Johnson & Johnson) to Flixabi, compared with those who continued on Remicade. Benepali and Flixabi were approved by the European Commission earlier this year. (See *BioWorld Today*, Jan. 20, 2016, and June 1, 2016.)

Sophiris Bio Inc., of La Jolla, Calif., disclosed biopsy results from all 18 patients enrolled in the phase IIa proof-of-concept study of topsalysin in localized prostate cancer. The one-time administration of topsalysin was well tolerated with no serious adverse events and no new safety signals being reported. Topsalysin demonstrated an ability to ablate tumor cells in 50 percent of patients (9/18 patients) six months after treatment in a patient population with pre-identified, clinically significant prostate cancer. The results support advancing topsalysin into a phase II study to confirm dose and optimize delivery, the company said. Topsalysin, an inactivated pore-forming protein, was engineered to be activated only by enzymatically-active PSA, which is present only in prostate tissue. The company's stock (NASDAQ:SPHS) closed at $1.17 Thursday, up 9 cents. The news was released just after the market closed and the stock shot up as high as 125 percent in after-hours trading.

Tonix Pharmaceuticals Holding Corp., of New York, presented results from a retrospective analysis from its phase IIb BESTFIT clinical study further supporting TNX-102 SL (cyclobenzaprine HCl sublingual tablets) 2.8 mg for the treatment of fibromyalgia. Data were featured in a poster presentation at the European League Against Rheumatism. The retrospective analysis clearly demonstrates improvements in the key domains of fibromyalgia and shows that TNX-102 SL has broad activity confirmed by different experimental responder analyses, the company said.