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Multitarget bid with sequencing

Lodo's soil-DNA approach hits pay dirt in Roche deal, value set as high as $969M

By Randy Osborne, Staff Writer

Lodo Therapeutics Corp. chalked up with Roche Holding AG's Genentech arm its first major deal for a platform that involves making bioactive natural products directly from the microbial DNA sequence information contained in soil, with Genentech pledging as much as $969 million, which includes an up-front payment of an undisclosed amount.

See Lodo, page 3

In the public markets

Evelo rides biopharma IPO wave, raises $85M to disrupt disease with monoclonal microbials

By Marie Powers, News Editor

Evelo Biosciences Inc., which is seeking to piggyback on the natural evolution of the gut to disrupt disease processes, raised $85 million in its IPO by offering approximately 5.3 million shares priced at $16 – the midpoint of its proposed range – to advance its microbial gut therapies, which target inflammatory diseases and cancer. The company, which listed on Nasdaq under the ticker EVLO, granted underwriters a 30-day option to purchase up to 796,875 additional shares, potentially adding $12.75 million to its raise.

Evelo had some help from insiders, which, according to an amendment to its S-1 filing, expressed interest in purchasing approximately $40 million of the IPO shares.

The Flagship Pioneering company emerged in 2014

See Evelo, page 4

Bioclin lands expanded $50M series B for trials of anti-FGFR3 candidate in bladder cancer

By Michael Fitzhugh, Staff Writer

Bioclin Therapeutics Inc., a startup developing a monoclonal antibody (MAb) to fight metastatic bladder cancer, has expanded its series B financing to $50 million. Proceeds from the round will be used to support phase II testing of the

See Bioclin, page 5

Under 'surveillance' for 15 years

Escient prescient? MGPRs' potential garners series A: $40M for preclinical-stage

By Randy Osborne, Staff Writer

Escient Pharmaceuticals Inc. CEO Alain Baron told *BioWorld* that the company's $40 million in series A cash will "take us through 2021, we believe, and we expect to be in the clinic in that time in at least

See Escient, page 7

Ascletis becomes first biopharma to file under new HKEX listing rules

By Elise Mak, Staff Writer

HONG KONG – Hangzhou, China-based Ascletis Pharma Inc. became the first pre-revenue biotech startup to seek public listing in Hong Kong this week. The company plans to use the proceeds to advance its two hepatitis C drug candidates into commercialization in China.

See Ascletis, page 9

Cochrane meta-analysis debunks health scares linked to HPV vaccines

By Nuala Moran, Staff Writer

LONDON – Claims that human papillomavirus (HPV) vaccines cause harm have been shown to be unjustified in a meta-analysis of 26 trials involving more than 73,000 girls and women, published this week.

See HPV, page 6

What's happening at Sinovac? Vaccine business disrupted by dispute over privatization

By Elise Mak, Staff Writer

HONG KONG – Nasdaq-listed Chinese vaccine maker Sinovac Biotech Ltd. is on the brink of collapse, as it is undergoing a series of events due to internal disputes concerning its privatization. The company has put its vaccine productions on

See Sinovac, page 8

Newco News

Memo from self: Swiss startup raises $5M for antibody library technology

By Cormac Sheridan, Staff Writer

DUBLIN – Early stage Swiss firm Memo Therapeutics AG raised CHF5 million (US$5 million) in a series A2 round to fund preclinical development of its antibody discovery platform,

See Memo, page 10

Other news to note

Acelrx Pharmaceuticals Inc., of Redwood City, Calif., resubmitted the NDA for Dsuvia (sufentanil sublingual tablet) to the FDA and anticipates that the agency will acknowledge acceptance within 30 calendar days. The company expects a six-month review, with a PDUFA date in the fourth quarter of this year. Dsuvia bears a proposed indication for the management of moderate to severe acute pain in medically supervised settings, in adult patients. In October, a complete response letter from the FDA said regulators wanted more information about dosing and about directions to prevent mishaps with the device associated with the drug. (See *BioWorld*, Oct. 13, 2017.)

Axial Biotherapeutics Inc., of Boston, presented preclinical data at the International Society for Autism Research conference in de Doelen ICC Rotterdam, the Netherlands, showing that concentrations of the bacterial metabolite, 4-ethylphenylsulfate, or 4-EPS, were elevated as much as sixfold in serum samples from children with autism spectrum disorder compared to healthy controls in replicate analyses. Axial is developing therapeutics based on the link between the human gut microbiome and the central nervous system.

Biohaven Pharmaceutical Holding Co. Ltd., of New Haven, Conn., established an expanded access program with sublingual BHV-0223, an investigational drug candidate, for patients with amyotrophic lateral sclerosis (ALS). Through the program, physicians may be able to obtain BHV-0223 for their eligible patients with ALS at no cost. BHV-0223 is a sublingual and lower-dose formulation of riluzole that employs the Zydis orally dissolving tablet technology and does not require swallowing tablets or additional fluids. The active ingredient riluzole is the only approved drug therapy for ALS shown to prolong survival, Biohaven said, and the firm anticipates submitting an NDA in the third quarter of this year.

Earnings

Flexion Therapeutics Inc., of Burlington, Mass., reported first-quarter sales of Zilretta (triamcinolone acetonide extended-release injectable suspension), approved in October for osteoarthritis knee pain, of $2.2 million. Net loss was $41.6 million for the quarter. As of March 31, the company had about $376.6 million in cash, equivalents and marketable securities. Shares of Flexion (NASDAQ:FLXN) closed Wednesday at $25.43, down 31 cents.

Jazz Pharmaceuticals plc, of Dublin, reported revenues of $444.6 million for the first quarter, including sales of narcolepsy drug Xyrem (sodium oxybate) totaling $316.8 million, up 16 percent over the first quarter of 2017. Sales of both cancer drug Erwinaze/Erwinase (asparaginase Erwinia chrysanthemi) and hepato veno-occlusive disease drug Defitelio (defibrotide sodium) dropped slightly over the same period last year, totaling $50.6 million and $35.1 million, respectively. Vyxeos (daunorubicin and cytarabine), which gained approval for acute myeloid leukemia in August, had sales of $26.2 million for the first quarter. GAAP net income for the quarter was $46 million, or 75 cents per share. As of March 31, Jazz had $453.2 million in cash and equivalents. Company shares (NASDAQ:JAZZ) closed Wednesday at $156.31, up $8.75.

Melinta Therapeutics Inc., of New Haven, Conn., reported revenue of $14.8 million for the first quarter, including product sales of $11.8 million. Its marketed products include Baxdela (delafloxacin), Vabomere (meropenem and vaborbactam), Orbactiv (oritavancin) and Minocin (minocycline) for injection. Net loss for the quarter was $29.4 million, or 95 cents per share. Melinta ended the quarter with cash and equivalents totaling $91.5 million. Shares (NASDAQ:MLNT) closed Wednesday at $7.50, up 5 cents.

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Lodo

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"The real differentiating factor, I suppose, for our approach vs. others out there that are working in the genomics area is that we look at pretty much the entire potential metabolic output of bacteria, because we don't have to culture bacteria before we isolate the DNA" since the firm uses a sequence-based approach, David Pompliano, chief scientific officer and co-founder of New York-based Lodo, told *BioWorld*. "We take soil samples, and we basically just extract all the DNA we can out of it. Soil samples can have thousands and thousands of species, most of which – in fact less than 1 percent of which – are actually culturable under normal laboratory conditions. That means we have access to potentially 99 percent of the molecules that bacteria might have made if they could have been cultured."

> *"We have access to potentially 99 percent of the molecules that bacteria might have made if they could have been cultured."*
>
> David Pompliano
> CSO and co-founder, Lodo Therapeutics

The multitarget arrangement with Roche includes research, development and commercialization milestone payments, along with tiered royalties on sales. He declined to provide specifics of the terms.

"We basically take detergent and extract all the DNA out of the soil [sample]," which includes bacteria, fungi and more, Pompliano said. "Gene clusters that encode molecules tend to be in one place instead of scattered around the genome," hence the bacterial focus. Researchers use degenerate polymerase chain reaction as a "way of identifying short stretches that might be conserved amongst the genes that encode metabolic pathways we're looking for," he said.

The company was founded about two and a half years ago on the findings of Sean Brady at Rockefeller University. Backed by Accelerator Life Science Partners and the Bill and Melinda Gates Foundation – with the latter, Lodo is working on tuberculosis therapies – Lodo takes its name from the Spanish word for mud and lists 15 employees on the roster, though the number is expected to grow. Industry backers include the likes of Abbvie Inc., Eli Lilly and Co. and Johnson & Johnson.

Brady's group had worked for about a decade on methods to access the chemical and biosynthetic potential of uncultured, previously inaccessible bacteria directly from environmental samples, a field known as metagenomics. A meeting with the Gates group led to that collaboration, right around the time when Accelerator was making itself known in New York. Lodo garnered $17 million in a series A round at the start of 2016. (See *BioWorld Today*, Jan. 11, 2016.)

The series A "enabled us to get through all the necessary work" and decide on a preclinical development candidate, and "a couple of other projects [are] not quite that far advanced," Pompliano said.

Another company that works in a somewhat similar mode is Cambridge, Mass.-based Warp Drive Bio Inc., "but they work only on cultured bacteria," he said. "We have no such limitation."

Warp Drive has a deal with Basel, Switzerland-based Roche, too. Entered in the fall of 2017, the pact has Warp deploying its Genome Mining platform to advance new classes of antibiotics with activity against drug-resistant, gram-negative pathogens. Warp said it's identifying and evaluating more than 100 novel classes of potential antibiotics that were previously undiscovered and thus never analyzed. (See *BioWorld*, Oct. 16, 2017.)

Some academic groups are working in the Lodo's general space, but none is bacterial-focused.

There's also Hexagon Bio Inc., of Menlo Park, Calif., which ransacks fungal genome data for possible drug applications. "That's a different approach because of the nature of the genome," Pompliano noted.

Last September, another fungi-focused genomics firm, Boston-based Lifemine Therapeutics Inc. followed up its $5 million seed round, quietly raised the previous year, with a $55 million series A round. The company was co-founded by Harvard Medical School professor, serial entrepreneur and investor Gregory Verdine. (See *BioWorld*, Sept. 19, 2017.) ♦

Other news to note

Durect Corp.. of Cupertino, Calif., entered an amendment to the development and commercialization agreement with Sandoz AG, a division of **Novartis AG**, of Basel, Switzerland, regarding Posimir (Saber-bupivacaine) in the U.S. Pursuant to the amended agreement, Durect is now eligible for up to $30 million in milestone payments based on NDA approval, and remains eligible for up to an additional $230 million in sales-based milestones. Each party, pursuant to the amendment, is also permitted to develop or commercialize competing products. The amendment also includes modifications to Durect's development obligations and to both parties' termination provisions, including a right for Durect to terminate for convenience prior to NDA approval. There is also a new termination fee payable to Durect in the event that Sandoz terminates the agreement for convenience. (See *BioWorld*, Oct. 23, 2017.)

Forma Therapeutics Inc., of Watertown, Mass., and the University of Oxford entered a collaboration and license agreement to identify, validate and develop deubiquitinating enzyme (DUB) inhibitors for the treatment of neurodegenerative diseases. DUBs are a family of more than 100 proteases that play roles in protein and cellular homeostasis. Under the terms, Forma will fund a multiyear research program at the university focusing on DUBs implicated in the pathogenesis of neurodegenerative disease, and will have the right to develop and commercialize DUB inhibitors studied under the collaboration.

Evelo

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from the Venturelabs unit with the goal of identifying, characterizing and understanding the biology of cancer-associated bacteria. Armed with $35 million from Flagship, the Cambridge, Mass.-based company began to explore ways to leverage the ability of bacteria to activate the immune system to fight cancer by targeting the gut-body network.

"The opportunity we see is a range of new therapeutic approaches that are going after this axis between the gut microbiome – through immunology and through metabolism – and another foreign entity living inside our bodies: cancer," Flagship senior managing partner and CEO Noubar Afeyan told *BioWorld* at the time. (See *BioWorld Today*, Nov. 4, 2015.)

Evelo became the third microbiome-focused company to emerge from Venturelabs, following Seres Therapeutics Inc. and the agriculture-focused Symbiota LLC.

Evelo's so-called monoclonal microbials are orally delivered pharmaceutical compositions of strains of naturally occurring microbes, derived from a single clone, that are designed to act on the gut-body network. Preclinically, the company showed that certain monoclonal microbials can down-regulate or up-regulate immune responses throughout the body by acting on the gut-body network.

Last month, the company moved its lead inflammatory disease candidate, EDP-1066, into a phase I safety and tolerability study in 36 healthy volunteers and in 60 patients with psoriasis or atopic dermatitis. The trial is testing a range of daily doses across 14 days in healthy volunteers and 28 days in patients. Although safety is the primary endpoint, the study also is assessing pharmacodynamic markers, including biomarker signals from paired biopsies of affected skin in patients, as secondary endpoints. Initial biomarker and clinical data are expected to report in the first half of 2019.

Third biopharma IPO pricing in 2Q

A second candidate, EDP-1815, is expected to begin phase I studies in the fourth quarter. Preclinically, EDP-1815 showed immunomodulatory activity on human immune cells and anti-inflammatory activity in discrete tissues, including skin, joints, gut and the central nervous system. Evelo expects to report initial data from that program in the second half of 2019.

Evelo's first oncology candidate, EDP-1503, is expected to begin human trials in the second half of the year into early next year, with initial data expected in 2020.

In its filing, Evelo said it plans to apply proceeds from the IPO, together with approximately $114.3 million in cash and equivalents as of March 31, to fund proof-of-concept studies in its inflammatory disease and oncology programs, to invest in its platform and to advance additional preclinical candidates.

Evelo is led by serial investor and entrepreneur Simba Gill, president and CEO, who also serves as a Flagship senior partner. With a track record in biotech and big pharma, Mark Bodmer, president of R&D and chief scientific officer, was involved at the ground floor of therapeutic humanized antibodies as a project leader at Celltech Group plc, acquired in 2004 by UCB SA for $2.7 billion in cash. Duncan McHale, hired this year as chief medical officer, also hails from UCB, where he served as head of global exploratory development, following roles at Astrazeneca plc and Pfizer Inc.

Afeyan chairs the company's board.

Morgan Stanley, Cowen and Co. and BMO Capital Markets are lead managers on the offering.

On its initial trading day, Evelo's shares hit $16.40 before closing at $16.25.

Evelo is the third U.S. biopharma to price its IPO in the second quarter. In April, Surface Oncology Inc. (NASDAQ:SURF) raised $108 million in its upsized IPO to advance its immuno-oncology pipeline. (See *BioWorld*, April 20, 2018.)

Earlier this month, Unity Biotechnology Inc. priced its IPO of 5 million shares at $17 apiece, the midpoint of its proposed range, to raise $85 million for its pipeline of therapies to treat aging-related diseases, beginning with osteoarthritis of the knee, through selective elimination of senescent cells.

Four additional U.S. biopharmas remain in the IPO queue, according to *BioWorld* Snapshots, where they're outpaced by eight ex-U.S. companies seeking to list their American depositary shares in the U.S. – joining Morphosys AG (NASDAQ:MOR), which completed its U.S. IPO in April – or to register their shares on a foreign exchange. (See *BioWorld*, April 4, 2018, April 20, 2018, and April 30, 2018.) ♦

Other news to note

Gilead Sciences Inc., of Foster City, Calif., was the target of a personal injury lawsuit and a separate class action lawsuit seeking to hold the firm accountable for what are claimed to be actions around its failure to rectify a known defect in the drug formulation of Viread (tenofovir disoproxil fumarate), knowing a safer alternate existed. Also alleged is a failure to warn patients of the damaging side effects and active misrepresentation of the drug's efficacy and risks. The legal actions, prepared by Rutherford Law attorney Michelle Rutherford and in-house counsel for the AIDS Healthcare Foundation, were filed in Superior Court of the State of California for the County of Los Angeles.

Igem Therapeutics Ltd., of London, disclosed the award of a £1.45 million (US$1.9 million) grant from the U.K.'s innovation agency, Innovate UK. Igem will use the Biomedical Catalyst award to further the development of IGEM-Ch, an IgE antibody targeting solid tumors. The compound specifically is a humanized IgE antibody that binds to the cancer antigen CSPG4 (chondroitin sulphate proteoglycan 4), overexpressed in melanoma and various other cancers, including triple-negative breast cancer.

Bioclin

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company's lead candidate, B-701, both as a single agent as well as in combination with Keytruda (pembrolizumab, Merck & Co. Inc.) and separately with docetaxel. Enrollment in phase II trials of the anti-fibroblast growth factor receptor-3 (FGFR3) MAb is expected to wrap up by the second half of 2018, with initial data expected by year-end, said Stephen Lau, CEO of the San Leandro, Calif.-based venture.

New investors Sectoral Asset Management and Inkef Capital joined existing investors Sofinnova Ventures, Ysios Capital, Healthcap, Tekla Capital Management funds and Life Sciences Partners in the round. The series B close, which initially totaled $30 million in March 2017, brings the company's total raise to $79 million.

Lau founded Bioclin in 2013 to focus on diseases with no approved or effective therapies. His initial focus was on using B-701 to treat achondroplasia, a bone growth disorder that is the most common cause of short-limbed dwarfism. But the entry of rare disease powerhouse Biomarin Pharmaceutical Inc. into achondroplasia with vosoritide prompted a reconsideration of the company's direction. At the same time, evidence arguing for B-701's advancement in bladder cancer was building, adding further weight to an earlier chapter of the candidate's story.

Preclinical data generated by Genentech Inc. as early as 2009 suggested that knockdown of FGFR3 in human bladder carcinoma cells could have a positive impact on progression of the disease. However, because a phase I study that followed didn't end up including participants with FGFR3 overexpression or mutation and — at the time — no clinical evidence supported further pursuit of the idea, exploration of that avenue landed on pause.

In the years that followed, further explorations of pan-FGF inhibition in other quarters advanced the story for the class, revealing that selecting metastatic bladder patients for FGFR3 abnormalities led to tumor response.

Nowhere has the story unfolded more robustly than at Janssen Biotech Inc., a subsidiary of New Brunswick, N.J.-based Johnson & Johnson, which has advanced its oral pan-FGFR inhibitor, erdafitinib, through phase II for metastatic urothelial cancer. Its phase II study, BLC2001, presented at the 2018 ASCO Genitourinary Cancers Symposium, showed an overall response rate of 42 percent in 59 patients with relapsed/refractory metastatic urothelial cancer whose tumors harbored actionable FGFR mutations.

Meanwhile, some checkpoint inhibitors have also shown progress in improving treatment in bladder cancer, lifting response rates into the realm of one-in-five to one-in-six patients vs. the one-in-10 response rate typically seen with chemotherapy. While Genentech's own PD-1/PD-L1 inhibitor, Tecentriq (atezolizumab), seemed to be a leader in that story, it later failed a confirmatory trial in the indication just after Bioclin had made plans to test B-701 with it. (See *BioWorld Today*, May 11, 2017.)

Now, with the efficacy of FGFR inhibition and the checkpoint story having both come into better focus, Bioclin is moving ahead. Last year, the company presented data from a phase Ib study enrolling patients with metastatic bladder cancer in which six patients with FGFR3 mutation/fusion were treated with B-701 plus docetaxel. The trial showed that the combination resulted in stable disease for six months and that there was a tumor response in about a third of patients.

New phase II studies will include only patients preselected with an FGFR3 mutation/fusion. In one of the trials, one cohort will enroll patients receiving monotherapy. This cohort, with expansion, could potentially serve to support accelerated approval, Lau said. A second cohort will look at B-701 with chemotherapy, while a third separate trial will test B-701 in combination with Keytruda.

"I think we're in a very interesting place. When you're in such a late-stage disease, physicians want to do combination therapies. There's really scientific rationale for pushing down FGFR3 to make these immune checkpoint drugs work better," Lau said.

Bladder cancer is the ninth most frequently diagnosed cancer worldwide, and the 13th most deadly, according to a Cortellis Disease Briefing. ♦

Other news to note

Insys Therapeutics Inc., of Phoenix, agreed to an exclusive license partnership with **Lunatus**, of Dubai, India, for commercialization of Subsys (fentanyl sublingual spray) in the Middle East. Lunatus will be the exclusive licensee for Subsys in Bahrain, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia and the United Arab Emirates. Under the terms of the partnership, Insys' responsibilities will include supplying Subsys to Lunatus, whose responsibilities will include obtaining the required regulatory approvals to commercialize the drug in the licensed territory.

Intellipharmaceutics International Inc., of Toronto, commenced its category 2 and 3 human abuse liability studies for the company's Oxycodone ER (oxycodone hydrochloride extended-release formulation) product candidate to support its abuse-deterrent label claims for the intranasal route of administration. The company's NDA was accepted for filing by the FDA in February 2017. The submission was supported by category 1 abuse-deterrent studies (to support intravenous abuse-deterrent label claim) and pivotal pharmacokinetic studies that demonstrated that the product is bioequivalent to Oxycontin (oxycodone hydrochloride extended-release, Purdue Pharma LP) and can be administered with or without a meal (i.e., no food effect). A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee of the FDA held in July 2017 expressed a desire to review additional data for Oxycodone ER that may be obtained from human abuse potential studies for the oral and intranasal routes of administration, the company noted.

HPV

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The review failed to find any evidence the vaccines cause serious side effects and concluded that Merck & Co. Inc.'s Gardasil and Glaxosmithkline plc's Cervarix protect against cervical lesions and are particularly effective in those vaccinated between the ages of 15 and 26.

The risk of serious adverse events was similar between controls and HPV groups in women of all ages, at 669 per 10,000 in controls vs. 656 in subjects receiving HPV vaccination.

Mortality was 11 per 10,000 in controls vs. 14 per 10,000 in vaccinated groups. However, none of the deaths reported in the studies have been judged to be related to the vaccine.

In addition, there was no increased risk of miscarriage or congenital abnormalities in babies born to women who became pregnant during the studies.

The analysis, carried out by the independent Cochrane network of health researchers, confirms the findings of other international monitoring agencies. That includes seven reviews by the World Health Organization's Global Advisory Committee for Vaccines Safety, none of which have found any cause for concern.

Health officials in a number of countries have become concerned that anti-vaccination campaigns are undermining public confidence in HPV immunization. For example, rates of vaccination have fallen in Denmark, Ireland and Japan, following scares about a range of adverse events that have been blamed on those vaccines.

Between 2014 and 2016, HPV vaccination coverage among 12-year-old Danish girls fell dramatically, from around 90 percent to below 40 percent.

A survey carried out by the Danish Health Authority in 2016 found that nearly all parents who were unsure about whether their daughters should be vaccinated were concerned about media reports of symptoms, including pain and tiredness, in girls who had the vaccine.

That led the Danish government to ask the EMA to carry out a safety review and in particular to look into reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS), in young women given HPV vaccines.

Symptoms of CRPS and POTS overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. However, the EMA found no evidence that the overall rates of those syndromes in vaccinated girls were different from expected rates in those age groups, even taking into account possible underreporting.

In 2017, the Danish Health Authority, the Danish Cancer Society and the Danish Medical Association launched a joint campaign to rebuild confidence in HPV vaccines and remind people the risk of getting cervical cancer far outweighs the risk of adverse vaccine events.

Uptake has now increased, and in 2017 around 31,000 girls started the HPV vaccination program, compared to just over 15,000 in 2016.

There is a similar picture in Ireland, where uptake of HPV vaccines fell from 87 percent to 50 percent, as a result of similar scares. A Health Service Executive campaign launched in September 2017 has had some success, with two out of three eligible girls now getting vaccinated.

In Japan, case reports of CRPS and POTS in some girls who received HPV vaccines led the government to suspend the recommendation for routine use. A national expert committee concluded the symptoms were not caused by HPV vaccination, but rate of HPV immunization in the country has fallen from 70 percent in 2013, to 1 percent.

> *"The fact that we now have a vaccine that can safely reduce the likelihood of women developing cervical lesions, which often lead to cervical cancer, should be greeted with the highest level of enthusiasm."*
>
> Peter Openshaw
> President, British Society for Immunology

'Completely unfounded'

Although there have been a number of previous reviews of HPV vaccination, covering millions of subjects, none of those have combined information on all available endpoints, as the Cochrane review published this week does.

That is important because the work provides a template for reporting future results. In addition, the reviewers said they made "a particular effort" to assess the cause of severe adverse events.

"The negative press that the vaccine has received in some countries is completely unfounded on evidence," said Peter Openshaw, president of the British Society for Immunology, commenting on the analysis.

Not only that, the Cochrane research highlights the huge public health benefits. "This very comprehensive review found that the HPV vaccine protects against precancerous changes in the cervix, particularly when given to women aged 15 to 26," Openshaw said. "The fact that we now have a vaccine that can safely reduce the likelihood of women developing cervical lesions, which often lead to cervical cancer, should be greeted with the highest level of enthusiasm."

Mary Ramsay, head of immunization at the health authority Public Health England, agreed the Cochrane study adds to "the wealth of growing evidence from around the world" showing HPV vaccines are the best way to protect against cervical cancer.

Most women ages 15 to 25 in the U.K. have been immunized, and epidemiological data collected by Public Health England show there has been a significant decrease in the prevalence of HPV 16 and 18, the two main cancer-causing variants of the virus, Ramsay said.

The Cochrane review showed that for girls who were HPV-negative at the time of vaccination, the risk of cervical lesions was reduced from 164 per 10,000 to two per 10,000. For those infected with HPV at the point of vaccination, the risk fell from 341 per 10,000 to 157 per 10,000.

Progression from HPV infection to invasive cancer takes a minimum of 10 years and the duration of follow-up in the trials included in the review is too short to show if HPV vaccines are effective in preventing cancer. ♦

Escient

Continued from page 1

one indication, and perhaps even as far as proof of concept in one indication."

The San Diego-based firm is working with G protein-coupled receptor (GPCR)-targeted therapies in varied indications, focused especially on orphan GPCRs, including Mas-related G protein receptors (MGPRs). Programs are based on the research of Xinzhong Dong, a Howard Hughes Medical Institute investigator and professor of neuroscience at Johns Hopkins University School of Medicine.

"The best way to describe [the eight known MGPRs] at this stage of knowledge is that they are surveillance receptors," Baron said, comparing them to innate immune system receptors that "detect patterns of chemicals that are extant in the environment. Very much like the innate immune system, these receptors are there to detect stimuli from the external as well as the internal environment. They transduce a reaction, which can be a disease or a syndrome. To date, no therapy has been brought to bear to treat these syndromes or diseases with a direct knowledge of the underlying mechanism of action."

Escient will take aim first at two MGPRs, exploring therapies for neuro-immuno-inflammatory and autoreactive diseases, though Baron would not say which ones. "Some are rare and some are not so rare," he said, adding that in some cases they have "not been classified properly. There's really no literature that you could go to on these receptors," since it's as-yet unpublished, he said, though MGPRs in question involve diseases for which only supportive or palliative care is available.

Neuro-immunology, on which *Science* published a recent article, is a "newly coined axis," Baron said. One might think of the immune system attacking the neural system, as in multiple sclerosis, but "what we're talking about is actually the reverse of that, although there may be some two-way arrows in the system," he said. Complicating the picture still further, "some diseases have been characterized as immune, but they have some neural basis, and some neural diseases may have some immune basis," he said. "It's confusing to the physicians, because you have markers of both, but you don't know exactly how to treat them."

Escient may have found the key.

"One of the difficulties in the field is that typically, when you have a human gene of interest, you try to identify the ortholog in the mouse," Baron said. "You knock it out, you knock it in, and then you get a sense of the biology and what it might do, transduce, and what have you." But the mouse has "somewhere north of 40 copies of these things," he said. "A lot of them are pseudo-genes and duplicate genes, and the homology between the human genes, in many cases, and mouse genes is very poor. While they're recognizable as MGPRs, they're not as readily matched one-for-one between the human and the mouse, which makes it virtually impossible to study in the mouse."

Baron said Dong took a different tack to identify the mouse ortholog. "He has these animals that either overexpress or are knocked out for that particular MGPR, or he has humanized the mouse, where he's knocked out the mouse ortholog and put in the human," he said. "You can study the role of the human receptor in its mouse ortholog in vivo, and then you can query as to what it might do in this tissue or that tissue. We're talking about really painstaking work. It took at least 15 years."

Very few other labs are exploring the area, he said, "and those labs have actually collaborated with [Dong] in most cases. He's got the animals, he's got the reagents, and all that stuff. It's one of these rare finds, frankly, where you have a mother lode of novel GPCRs, largely ignored because of the difficulty in de-orphaning them."

Baron described MGPRs as "pretty classic, responding to small molecules. We have no reason to think that they're not readily druggable, but as we speak we don't know that for a fact. We'll know very soon."

Meanwhile, it's apparent that they "behave and look very much like garden-variety GPCRs," he said. The diseases they will target are serious and symptomatic. "Unlike [in] chronic diseases, where you want to see some efficacy over time and some evolution in the biology, here we should be in many cases able to see very rapid responses, if our drugs do what they are supposed to do," he said. "The proof-of-concept part, which is really the value inflection that we're all looking for, can be readily obtained with the kinds of clinical states that these receptors, we believe, are responsible for." That could mean smaller-scale experiments, although regulators must yet be consulted. "Anytime you have something new, the agency needs to think about it," he said.

Escient list four employees, with an offer out to another prospect. By leaving stealth mode, the company hopes to draw top biologists, chemists and executives. "Over the next 12 to 18 months, we expect to have between 15 and 20 people," Baron said.

The company deploys a hybrid organic-outsourced model, one that Marcus Boehm, co-founder of Escient, used during his six-year tenure as chief technology officer at San Diego-based Receptos Inc. before Celgene Corp., of Summit, N.J., bought the firm for $7.2 billion. "It's fair to say that for every organic employee that Escient will have, we'll probably have two outsourced" workers, he said. Exploratory and discovery efforts will be kept in-house. (See *BioWorld Today*, July 16, 2015.)

The name of the company is born of "necessity and elimination," Baron said. "It's almost impossible these days to find a proprietary name that hasn't been taken." Deriving from a French word, Escient is meant to connote good judgment, wisdom, knowledge, awareness – and perspicacity, such as a surveillance receptor might be understood to show. Chosen as a logo for the firm was the owl, which "scans the environment in a very unique way" by virtue of its head swivel, he said.

Syndicated by The Column Group and 5AM Ventures, who were joined by Osage University Partners, the series A round showed what Baron called "forward thinking" by backers, a strong vote for early stage but promising discoveries. "The GPCR space has been really well trodden," he noted. "While there are about 100 or so still-orphan receptors, the notion that we can have eight that we can work on is just remarkable."

Sinovac

Continued from page 1

hold, which may soon have an impact on its business.

In the past few weeks, Sinovac's principal operating subsidiary, Sinovac Biotech Co. Ltd. (Sinovac Beijing), has been forced to destroy many of its vaccines because, according to the company, a team led by a company executive entered Sinovac Beijing's offices on April 17 and took a number of "aggressive actions," including "intentionally interfering with the audit of the company's financials, forcibly taking control of Sinovac Beijing's corporate offices and the Shangdi site, limiting the physical movement of the employees in Sinovac Beijing's general manager's office and finance department, cutting the power to the Shangdi site, disrupting Sinovac Beijing's hepatitis A and seasonal flu vaccine production, and forcing the company to destroy vaccines."

The company executive Sinovac blames for the disrupting behavior is Pan Aihua, who heads Sinobioway Biomedicine Co. Ltd., the minority shareholder of Sinovac.

"Sinovac's privatization is what leads to the developments these days," Cui Wenliang, analyst at Essence Securities, told *BioWorld*. "Sinovac plans to withdraw from the U.S. market to go public in China. Both sides want to seize control of the company."

Cui was referring to majority shareholder Sinovac Biotech (Hong Kong) Ltd. (Sinovac Hong Kong), which owns 73.09 percent equity interest in Sinovac Beijing. Sinobioway holds the remaining 26.91 percent.

"As the company goes private, a party can seek to expand its shareholding to get control of the target company," said Cui. A usual practice is to acquire 90 percent interest in the target company to secure the control.

The fight between the two shareholders has been going on since Sinovac announced the going-private proposal in 2016. A buyer consortium led by Yin Weidong, chairman of Sinovac Hong Kong, offered $7 per share in June 2017. Two days later, another consortium led by Pan raised the purchase price to $8 per share and accused Sinovac's special committee of colluding with Yin to stop others from joining the bid.

Pan argued that Sinobioway is the largest shareholder of Sinovac, since Yin himself only holds 10.61 percent out of the 73.09 percent stake held by Sinovac Hong Kong.

The latest development of the situation was an announcement by Sinovac on May 8, stating that the company had decided to destroy the bulk of its hepatitis A vaccines that could have produced around 3.5 million doses of finished products.

Sinovac's internal quality management regulations require the temperature of the refrigerator storing the vaccines inspected and recorded twice a day. As employees were unable to enter the facilities and perform the quality checks, the company could not guarantee the quality of vaccines – hence it chose to abandon them.

That was just another decision of Sinovac to destroy its vaccines. On April 30, the company halted production of its bacterial seeds for 23-valent pneumococcal polysaccharide vaccine (PPV), and later stopped producing flu vaccines on May 1.

Outlook unclear for now

It is still unclear, and probably very difficult to estimate, how much damage has been done to Sinovac financially.

"The company is not presently able to assess the impact on its sales of hepatitis A vaccine due to a lack of certainty regarding both the market's reaction to this incident, as well as the schedule for resuming production," noted the company in the statement.

In addition, Sinovac's annual audit of 2017 was also disrupted. The finance department was not able to function as the office building was blocked.

"Given what has been happening at Sinovac, its outlook has become not particularly promising even if it goes public in China," said Cui. "It is also no longer the biggest vaccine maker in China. Chongqing Zhifei Biological Products Co. Ltd., for example, is now performing better. Sinovac's shareholding structure is a mess, and the company will remain unchanged in nature."

But Zhou Shaogan, equity analyst at Founder Securities, told *BioWorld* that Sinovac still has a chance in the game.

"Its outlook is still promising. It's a big company after all," said Zhou. "Its value is currently underestimated in the U.S. When it returns to the Chinese market, its value will surge."

Dubbed as a top vaccine maker in China, Sinovac has an extensive product portfolio that includes vaccines against enterovirus71 (EV71), hepatitis A and B, seasonal influenza, avian flu, swine flu, mumps and canine rabies.

Sinovac developed the EV71 vaccine to treat hand foot and mouth disease. As only three companies are approved to manufacture such vaccine in China, EV71 holds vast potential for Sinovac, leading many to believe the company's value could go much higher.

Just before its vaccine-making business was seriously disrupted, the company was delivering positive updates on its products.

Sinovac announced positive results of a phase III study of its Sabin inactivated polio vaccine (sIPV) in mid-April and entered an agreement with the Netherlands' Intravacc to develop and commercialize sIPV for distribution to China and other countries. Its hepatitis A vaccine, Healive, was also accepted by the World Health Organization for purchase by United Nations agencies in December.

Shares of Sinovac (NASDAQ:SVA) closed Wednesday at $7.46, up 3 cents. ♦

Ascletis

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In March, the Hong Kong Stock Exchange (HKEX) said biotech companies that do not meet any of the Main Board financial eligibility tests could still seek listing in the city, opening the doors for startups with breakthrough innovations to a wider range of investors via the public financial markets. The new listing rules took effect on April 30. And Ascletis did not wait for long to take action. (See *BioWorld*, March 23, 2018, and April 26, 2018.)

A week after the HKEX officially lowered the listing bar, Ascletis filed its IPO application.

Focusing on fighting hepatitis C virus (HCV), HIV and hepatitis B virus (HBV), Ascletis now has seven drug candidates in its pipeline. Although none are commercialized yet, its two most advanced HCV drug candidates, danoprevir and ravidasvir, have both completed phase III trials. The company plans to launch danoprevir and file a new drug application for ravidasvir in the third quarter of this year.

According to the prospectus, danoprevir is the most advanced HCV treatment developed by a domestic company in China. The drug demonstrated a cure rate of 97 percent and a shorter treatment duration of 12 weeks in combination with pegylated interferon and ribavirin. Combining it with ravidasvir pushed the cure rate further up, to 99 percent.

Ascletis entered exclusive licensing agreements with pharma giant Roche Holding AG for danoprevir in April 2013 and with San Francisco-based Presidio Pharmaceuticals Inc. for ravidasvir in September 2014, which makes Ascletis the only Chinese company to develop, manufacture and market those drugs in greater China.

Besides the two near-commercial candidates, Ascletis' HIV drug, ASC-09, and liver cancer drug, ASC-06, have completed phase IIa and phase I trials, respectively.

At this time, the company is not disclosing information beyond its prospectus, Ascletis' associate director of corporate affairs, Wang Jianjiong, told *BioWorld*.

Yet while it's had clinical success, Ascletis is in need of capital to carry the firm forward into commercialization.

The prospectus showed that the drugmaker recorded losses mainly due to vast R&D expenditures in the past two years – ¥6.76 million (US$1 million) in 2016 and ¥131.85 million (US$20 million) in 2017. That makes Ascletis a fine example of how the new listing rules of the HKEX can help biotech startups that have high R&D costs but have yet to generate any revenue to raise funds from the market.

Caution needed

But analysts warn that investors should take caution when it comes to betting on biotech startups since most of them are not familiar with the industry.

"Without a track record of their revenue to use as reference, investors can take other things into consideration," Alfred Or, analyst at Finet Securities Ltd., told *BioWorld*.

"Things such as how much the company has put into R&D, how many of its research team members hold a doctoral degree, what products it makes and how many of them have entered phase III clinical trials, if the company works with established institutions, if it has patents and in-house technologies, its business model and so forth," explained Or.

"Individual investors are unlikely to invest in these pre-revenue biotech startups as most do not have the relevant knowledge. I assume interested parties would be left to private equity funds and venture capitals," he added.

However, Or said he also believes that Ascletis has its appeal to the investors as the first startup to file for IPO under the new listing regime.

"It has big names such as Morgan Stanley on its back and products that have entered phase III clinical trials. Ascletis is also developing drugs that treat cancer, which always see a great demand," said Or. "At this moment, the company seems to have potential."

According to Ascletis' prospectus, candidates danoprevir and ravidasvir will decide the fate of the company. It plans to allocate 25 percent of the proceeds to commercializing the two drugs, revenue from which will contribute to its financial prospects for the next few years, and another 30 percent to continue the R&D of its core product pipeline.

Ascletis aims to be the game-changer in HCV treatment in China, where there are 25.2 million estimated HCV-infected patients but the diagnosis rate "has historically been low due to the lack of awareness and effective treatment." The company estimated that China will see new infections of HCV rising to 410,000 in 2028 from 350,000 in 2017, representing a market with vast potential.

Before this IPO filing, Ascletis had previously secured $100 million in a series A private equity financing led by Hangzhou Binjiang Investment Holding in 2011, then another $100 million in the second round led by C-Bridge Capital in 2017. ♦

Other news to note

Krystal Biotech Inc., a gene therapy company developing an off-the-shelf therapy for dystrophic epidermolysis bullosa, said in vivo data on its lead gene therapy candidate, KB-103, demonstrated linear deposition of human functional COL7 in the basement membrane zone of hypomorph mice after injection. The study also found that human COL7 incorporates into anchoring fibrils with proper structural orientation; and that KB-103 exhibits expression and minimal in vivo toxicity after repeated administration. The data will be presented at the International Investigative Dermatology conference in Orlando, Fla.

Logicbio Therapeutics Inc., of Cambridge, Mass., initiated a development program targeting methylmalonic acidemia (MMA), a rare, life-threatening pediatric metabolic disease. Testing of LB-001, the company's preclinical pediatric genome editing therapy, will be accompanied by a natural history study of MMA in the next year intended to support the program as it advances toward an investigational new drug filing and clinical trial in 2019.

Memo

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which is based on a proprietary method of capturing and banking an individual's antibody repertoire.

Zurich-based Memo employs microfluidics and cell sorting technologies to isolate memory B cells directly from blood. Although the cells produce too little mRNA to support single-cell polymerase chain reaction (PCR) analysis, the company has developed a protocol – details of which are not yet in the public domain – that enables it to rapidly lyse the cells and capture low levels of mRNA encoding antibody chains. The resulting genetic information is stored in expression plasmids that can be expressed in either prokaryotic or human cell backgrounds. The approach extends beyond in silico analysis approaches associated with high-throughput sequencing.

"We think we are the only ones that express the library," Memo's founder and CEO Christoph Esslinger told *BioWorld*.

The company, a 2012 spin-out from ETH Zurich (Swiss Federal Institute of Technology in Zurich), operated initially as a virtual company before taking up space at ETH Zurich's incubator, the Innovation & Entrepreneurship Lab (IELab). Its core Memomab technology was developed jointly between the company and ETH Zurich, but it is now owned outright by Memo.

The company is addressing an issue that has long confounded researchers. Although an individual's memory B cells are, by necessity, long-lived, they remain quiescent unless exposed to an immune challenge – and are therefore difficult to cultivate ex vivo.

"The default option of B cells ex vivo is to die," Esslinger said. (That's why César Milstein and Georges Köhler developed the revolutionary hybridoma technology in the mid-1970s for the production of individual monoclonal antibodies.)

Esslinger became interested in the possibility of isolating human antibodies a decade and a half ago at the University of Zurich, while working with an antibody repertoire from an Alzheimer's disease patient who appeared to demonstrate a favorable response to a therapeutic vaccine directed at amyloid beta.

He subsequently became chief technology officer of another venture, CT Atlantic AG, which sought to capture antibody repertoires using Epstein-Barr virus (EBV) for conditional immortalization of memory B cells. "It's the same principle, but, I would say, inferior technology," he said. CT Atlantic's platform captured about 5 to 8 percent of any individual's antibody diversity. At present, Memo's platform can capture between 30 percent and 80 percent of an individual's antibody repertoire.

The company is "pretty happy" at the upper end of that range, Esslinger said. It opens up the possibility of discovering rare antibodies that may have relevance for human disease. The company's clinical strategy is based on analyzing the antibody repertoires of patients who have survived diseases, such as infection or cancer, on the basis that they may contain molecules that are highly protective. Human-derived antibodies have the added advantage that they are likely to be safe when administered to other patients, which speeds up toxicity testing. They are also highly potent. Those that Memo has isolated have picomolar affinities and are easy to produce at scale, Esslinger said.

The company is also using the platform to interrogate the antibody repertoires of rabbits, the current go-to species for generating highly diverse, potent and easy-to-manufacture antibodies.

Although the natural humoral immune response to pathogens typically involves a polyclonal collection of different antibodies, Memo is focusing on monoclonal antibodies for now, given the regulatory complexity attached to developing polyclonal therapies. Its lead program targets an undisclosed third-generation immune checkpoint, which is currently undergoing preclinical development.

"We expect to complete preclinical development by mid-2019," Esslinger said. It would then seek more cash – the present round is intended to bring the company to its next value inflection point – although it is open to the right preclinical licensing deal as well. Early stage talks with one potential partner are already in train.

Memo previously raised CHF2.3 million in a series A1 round. The present oversubscribed transaction attracted the participation of Schroder Adveq, the online investment platform investiere.ch and undisclosed private investors. Previous investors, including Redalpine Venture Partners, Zurich Cantonal Bank and additional private investors, also participated. ♦

Other news to note

Mannkind Corp., of Westlake Village, Calif., has negotiated an exclusive marketing and distribution agreement for its inhaled insulin product, Afrezza, in India with **Cipla Ltd.**, of Mumbai, India. Mannkind will receive a $2.2 million up-front payment from Cipla. Cipla will also be responsible for obtaining regulatory approvals to distribute Afrezza in India and will carry all marketing and sales costs in the country. Mannkind is responsible for supplying Afrezza to Cipla and is eligible to receive additional regulatory milestone payments, minimum purchase commitment revenue and royalties on Afrezza sales in India.

Palatin Technologies Inc., of Cranbury, N.J., reported new data on PL-8177, its lead candidate for the treatment of inflammatory bowel disease, and PL-8331, its candidate for the treatment of dry eye. Data from a rat model of bowel inflammation showed reduced inflammation and colon weight scores to a similar degree as sulfasalazine, the positive control drug, the company said. PL-8177 was also evaluated in a mouse model of autoimmune uveitis, in which it significantly reduced retinal inflammation compared to untreated controls. PL-8177 is in ongoing phase I studies. PL-8331 was evaluated in a mouse model of dry eye, in which it demonstrated reduction in corneal epithelial damage due to dry eye with efficacy similar to Restasis (cyclosporine, Allergan plc), the company said. Palatin anticipates completing investigational new drug application-enabling activities on PL-8331 later this year. The data were presented at the TIDES: Oligonucleotide and Peptide Therapeutics 2018 meeting in Boston.

Other news to note

Pharmacyte Biotech Inc., of Laguna Hills, Calif., said it successfully completed FDA-required "pore size studies" on its Cell-in-a Box capsules. As part of the company's investigational new drug application for its trial in patients with locally advanced, nonmetastatic, inoperable pancreatic cancer, the FDA required it to show that the size of the pores in the outer shell of the Cell-in-a-Box capsules is appropriate to allow ifosfamide to enter the interior of the capsules where the ifosfamide-activating cells are located and to allow the activated form of ifosfamide to leave the capsules.

Platelet Biogenesis Inc., of Cambridge, Mass., said it licensed patents related to induced pluripotent stem (iPS) cells from iPS Academia Japan's patent portfolio. Terms were not disclosed.

Protagen AG, of Dortmund, Germany, started a collaboration with the University of California, San Francisco, to utilize Protagen's Serotag technology to investigate the immuno-profiling of prostate cancer patients treated with checkpoint inhibitors and therapeutic vaccines. Terms were not disclosed.

Provention Bio Inc., of Oldwick, N.J., said it has struck a deal with **Macrogenics Inc.**, of Rockville, Md., to acquire all rights to teplizumab and licensing rights to MGD-010 for an undisclosed amount. The programs will now be advanced under the names PRV-031 and PRV-3279, respectively. Under the terms of the agreements, Macrogenics will receive a warrant to purchase a minority equity interest in Provention, and will be eligible to receive future milestone payments and royalties on future net sales. PRV-031, a humanized, anti-CD3 monoclonal antibody, is expected to enter pivotal phase III trials in late 2019 for early onset type 1 diabetes. PRV-3279, a humanized bispecific molecule that was designed to simultaneously target the B-cell surface proteins CD32B and CD79B, will advance in an ongoing multiple ascending-dose phase Ib/IIa study as a potential treatment for systemic lupus erythematosus.

Therapix Biosciences Ltd., of Tel Aviv, Israel, said its board has decided to take steps to voluntarily delist its ordinary shares from trading on the Tel Aviv Stock Exchange, while maintaining a continued listing of its American depositary shares on Nasdaq. The company said it's pursuing the move "in order to be subject to one set of listing regulations instead of two, to allow greater flexibility to execute its business and financing strategy and to reduce costs of operations."

Financings

Axogen Inc., of Alachua, Fla., priced a public offering of 3 million shares of common stock – upsized from the previously announced 2 million shares – at a price of $41 per share, for gross proceeds of about $123 million. Axogen granted underwriters a 30-day option to purchase up to an additional 450,000 shares, which could add about $18.5 million to the haul. Funds will be used for long-term facility and capacity expansion and general corporate purposes. Jefferies LLC and Leerink Partners LLC are acting as joint book-running managers, while William Blair & Co. LLC and JMP Securities LLC are acting as co-managers.

Cesca Therapeutics Inc., of Rancho Cordova, Calif., said in an S-1 filing that it is offering up to 3.2 million units – each unit consisting of one share of common stock and one common warrant to purchase one share of common stock. Units have not yet been priced. The company also is offering up to 3.2 million pre-funded units to purchasers whose purchase of units in the offering would otherwise result in the purchaser, together with its affiliates and certain related parties, beneficially owning more than 4.99 percent of outstanding common stock immediately following the consummation of the offering. The cell therapy firm plans to use net proceeds for general corporate purposes, including working capital.

Cstone Pharmaceuticals Co. Ltd., of Suzhou, China, said it completed a $260 million series B finding led by GIC Private Ltd., Singapore's sovereign wealth fund, with participation from new investors, including Sequoia China, Yunfeng Capital, 6 Dimensions Capital, CITIC PE, Taikang Insurance Group, Arch Venture Partners, Hillhouse Capital, King Star Capital, 3W Partners, Avict and Terra Mafnum Capital Partners. Existing investors also participated in the round, including Oriza Seed Venture Capital, Boyu Capital and Wuxi Healthcare Ventures (currently a 6 Dimensions Capital fund). Together with the $150 million raised in series A financing in 2016, the recent round brings the total capital raised to $410 million. Cstone, founded in 2016, is developing drugs and combination therapies in the immuno-oncology space. (See *BioWorld Today*, Oct. 24, 2016.)

Intelgenx Technologies Corp., of Saint Laurent, Quebec, closed its private placement, issuing 320 units at a subscription price of $10,000 per unit for gross proceeds of $3.2 million. The company intends to use the proceeds for its montelukast phase IIa trial and for general working capital purposes.

Lygenesis Inc., of Pittsburgh, raised $3 million in series A financing from Juvenescence Ltd. Lygenesis' technology uses lymph nodes as bioreactors to regrow functioning organs within a patient's own body. The financing will enable the company to complete the final preclinical work required to enable human clinical trials, which will initially focus on patients with end-stage liver disease.

Regulatory front

After news of its $1.2 million contract with Michael Cohen, a personal attorney for President Donald Trump, exploded this week across the headlines and in social media, **Novartis AG** issued a statement Wednesday basically saying there's nothing to see here other than the fact that the company got nothing for its money. The Basel, Switzerland-based drug company said it entered a one-year agreement with Cohen's firm, Essential Consultants, shortly after Trump took office last year to get insight as to how the new administration might approach certain U.S. health care policy matters, including the Affordable Care Act. Under the agreement, Novartis was to pay the consulting firm $100,000 a month. Following an initial meeting in March 2017, Novartis said it determined that Essential Consultants would not be able to provide the services it was seeking, so it didn't engage further with Cohen or the firm. However, the contract could only be terminated for cause, so Novartis continued to make the payments until the contract expired in February. Novartis said it was contacted last November by the Special Counsel's office regarding the agreement with Essential Consultants, and it provided all the information requested. "Novartis considers this matter closed as to itself and is not aware of any outstanding questions regarding the agreement," the company said.

Jazz Pharmaceuticals plc, of Dublin, reported it has reached an "agreement in principle" to pay $57 million to resolve a U.S. **Department of Justice** (DoJ) probe into its dealings with charitable organizations that help Medicare patients with out-of-pocket drug expenses. In its quarterly earnings report filed with the SEC Tuesday, Jazz said it reached the tentative agreement last month and has set aside $57 million for the civil settlement. The maker of the narcolepsy drug Xyrem (sodium oxybate) was one of several drug companies subpoenaed over the past few years over their support of the charitable organizations. Jazz said it has a comprehensive compliance program in place and has been cooperating with the DoJ investigation.

The U.S. **SEC** announced a settlement Tuesday with hedge fund advisory firm **Visium Asset Management LP** to resolve charges relating to asset mismarking and insider trading by its privately managed hedge funds and portfolio managers. The SEC found that certain Visium portfolio managers traded in the securities of pharmaceutical companies in advance of FDA approval of two generic drugs. Trades also were made in the securities of home health care providers prior to a proposed cut to certain Medicare reimbursement rates. The trades were based on confidential information from a former FDA official and a former Centers for Medicare & Medicaid Services employee who were both working as paid consultants to Visium, the SEC said. Under the settlement, Visium will disgorge more than $4.7 million in profits plus $720,711 in interest and pay a penalty of more than $4.7 million. Visium consented to the order without admitting or denying the findings.

The **FDA** is seeking public input as it revisits the framework, outlined in a draft 2012 guidance, for assessing drug-drug interactions (DDIs) for therapeutic proteins. Following the agency's systematic risk-based approach to DDIs, the 2012 draft recommended DDI assessment for therapeutic proteins that are cytokine or cytokine modulators, have a known or suspected mechanism of DDI not related to effects on cytochrome P450 enzymes or transporters, and are used in combination with another drug. In October, the FDA updated the 2012 draft by releasing two separate draft guidances on enzyme- and transporter-based DDIs, but neither of those guidances covers therapeutic proteins, according to a notice slated for publication in Thursday's *Federal Register*. The agency is requesting comments on which scenarios or classes of therapeutic proteins need a DDI assessment. It also is interested in study design considerations and the types of assessments that would be useful. Comments are due by July 9.

The **FDA** released a draft guidance on developing drugs for uncomplicated urinary tract infections. Reflecting recent scientific developments, the guidance defines trial enrollment criteria and provides trial design options to demonstrate efficacy. The draft fulfills an FDA Safety and Improvement Act provision that requires the agency to review and, as appropriate, revise at least three guidances per year for the conduct of clinical trials for antibacterial and antifungal drugs, according to a notice to be published in Thursday's *Federal Register*. The new guidance revises recommendations made in a 1998 draft that was withdrawn five years ago. Comments should be submitted by Aug. 8.

The **FDA** issued a question-and-answer (Q&A) guidance to help biopharma sponsors interpret the **International Council for Harmonisation**'s guidance *S3A Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies*. The Q&A discusses points to consider before using a microsampling method in toxicokinetic studies. It acknowledges the benefits and limitations of microsampling for assessing toxicokinetics in main study animals, as well as the overall contribution of microsampling to the 3Rs benefits (replacement, reduction and refinement) by reducing or eliminating the need for toxicokinetic satellite animals. Although the Q&A guidance is intended to apply to the majority of drugs, the FDA said, "consideration should be given on a case-by-case basis as to whether the sensitivity of the measurement method is appropriate for the small sample volumes available."

Australia's **Therapeutic Goods Administration** issued guidance Tuesday to help drug sponsors meet the country's requirements for child-resistant packaging (CRP) that went into effect in December. The guidance clarifies that CRP is not childproof; rather it is "intended to provide a delay in the time taken by a child to open a package, thereby increasing the probability of adult intervention before the contents are fully accessible," the TGA said. The guidance also notes that the CRP requirements apply to the drug package as a whole – not just individual components such as a bottle closure. The guidance discusses which drugs require CRP and the evidence needed to demonstrate that packaging is child-resistant. Sponsors have until Sept. 30 to comply with the new standards.

The **FDA** reported Tuesday that a Despir truck carrying partial lots of **Octapharma USA Inc.'s** Octagam 10 percent (immune globulin) was hijacked last week near Cornersville, Tenn., while en route to a customer in Alabama. The Hoboken, N.J.-based subsidiary of Octapharma AG is working with the FDA's Office of Criminal Investigations and other law enforcement officials to recover the stolen cases of the liquid solution intended for intravenous administration. The prescription drug is packaged in tamper-evident containers, so if a package has been opened, it will be evident to the consumer.

Clinical data for May 9, 2018

Company	Product	Description	Indication	Status
Phase I				
Miragen Therapeutics Inc., of Boulder, Colo.	Cobomarsen	MicroRNA-155 inhibitor	Mycosis fungoides form of cutaneous T-cell lymphoma	Cobomarsen improved quality of life, as measured by the Skindex-29 Total Score, with 13 of 18 patients showing improvement over the first 100 days on cobomarsen; at 1 year, 4 patients still had improvement and stabilization
Phase II				
Bonti Inc., of Newport Beach, Calif.	EB-001T	Botulinum neurotoxin serotype E	Postoperative pain	Started Latern-2 trial measuring postoperative pain at rest, as measured by the Numeric Pain Rating Scale, over the first 96 hours following abdominoplasty with plication of the RA sheath as the primary endpoint
Endocyte Inc., of West Lafayette, Ind.	177Lu-PSMA-617	PSMA-targeted radioligand therapy	PSMA-positive metastatic castration-resistant prostate cancer	Data from investigator-initiated trial of 30 patients published in *The Lancet Oncology* showed 57% of patients had a PSA reduction of at least 50% while 43% had a PSA reduction of at least 80%; median PSA progression-free survival was 7.6 months while overall survival was 13.5 months
Innovation Pharmaceuticals Inc., of Beverly, Mass.	Brilacidin	Synthetic mimic of host defense proteins	Severe oral mucositis in head and neck cancer patients receiving chemoradiation	In Brilacidin-OM trial, 42.9% of patients taking Brilacidin had severe oral mucositis compared to 60% of patients receiving placebo for the modified intent to treat population; in patients receiving 21-day high-dose cisplatin regimen, severe OM occurred in 25% and 71.4% of patients taking Brilacidin and placebo, respectively (p=0.048)
Ix Biopharma Ltd., of Singapore	Wafermine	NMDA channel blocker	Soft tissue postsurgical pain	Expanded KET010 trial to include separate cohort of 40 patients who have undergone abdominoplasty surgery
Restorbio Inc., of Boston	RTB-101	TORC1 inhibitor	Respiratory tract infections	Completed dosing of 652 elderly patients testing the drug alone or in combination with everolimus
Phase III				
Les Laboratoires Servier SAS, of Paris, and Taiho Pharmaceutical Co. Ltd., of Tokyo	Lonsurf	Nucleoside analogue and a thymidine phosphorylase inhibitor	Advanced metastatic gastric cancer	TAGS trial met its primary objective, showing improvement in overall survival for patients taking the drug compared to placebo

Notes

For more information about individual companies and/or products, see Cortellis.

Regulatory actions for May 9, 2018

Company	Product	Description	Indication	Status
Astrazeneca plc, of Cambridge, U.K.	Imfinzi (durvalumab)	Monoclonal antibody targeting PD-L1	Locally advanced, unresectable non-small-cell lung cancer	Health Canada approved the drug for patients whose disease has not progressed following platinum-based chemoradiation therapy
Cellectar Biosciences Inc., of Madison, Wis.	CLR-131	Phospholipid-drug conjugate	Rhabdomyo-sarcoma	FDA granted orphan designation
Lipocine Inc., of Salt Lake City	Tlando	Testosterone replacement therapy	Hypogonadism	FDA issued a complete response letter identifying four deficiencies that need to be rectified before approval

Notes

For more information about individual companies and/or products, see Cortellis.