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PAGE 1 OF 8

U.S. Biopharma Firms Hit By Cyber Attacks from China

By Shannon Ellis
Contributing Writer

SHANGHAI – While the presidents from the U.S. and China have met in a summit to address human rights and cyber-attack issues, it's become clear that U.S. biopharmaceutical firms have not been immune to targeted hacking out of China. These efforts may have yielded valuable data from clinical trials or drug registration applications.

Since the earliest identified cases in 2008, there has been a visible uptick in the number of hacking incidents involving biotech firms, according to Mandiant, a cyber-security consulting firm in the U.S.

The firm, the first to provide evidence of a coordinated hacking campaign by the Chinese government, said the number of hostile threats against biotech and pharmaceutical companies jumped to 4 percent of all the activity it responded to last year, up from 1 percent.

"In 80 percent of the network compromises Mandiant has observed in the biotechnology and pharmaceutical industries, the threat activity was associated with Chinese government-sponsored Advanced Persistent Threat [APT] groups," Senior Threat Analyst Laura Galante told *BioWorld Today*. There may be as many as 20 such groups operating in China.

Mandiant rose to prominence after it identified a specific

See Cyber Attacks, Page 3

BeiGene Inks $233M Deal With Merck for Cancer Drug

By Larry Schuster
Contributing Writer

SHANGHAI – BeiGene Co. Ltd. has licensed a second-generation BRAF inhibitor as a promising preclinical candidate oncology drug to Merck KGaA, of Darmstadt, Germany, for the treatment of melanoma, colorectal cancer and other cancers.

It marks what may be only the second instance of a Chinese company licensing a novel molecule to a multinational pharma firm. The first was the deal with

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Financings Roundup

AbbVie and Angels: Avaxia Closes $11M Series B for IBD

By Jennifer Boggs
Managing Editor

With data from the first clinical trial of anti-TNF polyclonal antibody AVX-470 in ulcerative colitis (UC) due toward the end of this year, Avaxia Biologics Inc. shored up its balance sheet with an additional $5 million, bringing its total Series B funding to $11.4 million.

As with past funding rounds, the Lexington, Mass.-

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Lots of Stomachs = Lots of Antibodies

Mushroom-Shape Cow Antibody May Broaden Therapeutic Reach

By Anette Breindl
Science Editor

Researchers have gained new insights into the structure of an unusual type of antibody that is made mainly by cows. They hope those insights will ultimately allow them to make antibodies for indications where traditional antibodies have not been successful.

In their work, which was published in the June 6, 2013,

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Repositioning Gains Momentum In Biopharma Partnerships

By Marie Powers
Staff Writer

Chronic fatigue syndrome (CFS) has been at the center of a vortex of controversy since the FDA handed down a complete response letter on the Toll-like receptor 3 modulator Ampligen (rintatolimod) from Hemispherx Bioscience Inc. – the only drug in development for CFS – despite the impassioned pleas of patients at an Arthritis Advisory Committee meeting in December 2012. (See *BioWorld Today*, Dec. 21, 2012, and Feb. 6, 2013.)

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Other News To Note

• **Advaxis Inc.**, submitted an application for orphan drug designation to the FDA for ADXS-HPV, its lead drug candidate, for the treatment of invasive cervical cancer.

• **Aeterna Zentaris Inc.**, of Quebec City, said the class action lawsuit filed against the company and certain of its officers by Faruqi & Faruqi LLP in the U.S. District Court for the Southern District of New York has been entirely dismissed with prejudice and without leave to amend. No payment was made by any of the defendants to the plaintiff or his counsel in connection with the lawsuit. The plaintiff has 30 days from the docketing of the final judgment to file a notice of appeal.

• **Affymax Inc.**, of Palo Alto, Calif., received a determination letter from Nasdaq delisting the company's common stock from Nasdaq as of June 6. Effective on that date, its common stock now trades for quotation on the OTCQB, an electronic quotation service operated by OTC Markets Group Inc. for eligible securities traded over-the-counter. The company expects that its common stock will also trade on the OTC Bulletin Board. Affymax will continue to trade under the symbol "AFFY." Also, Herb Cross was terminated as chief financial officer and an employee of the company. Rich Brenner of The Brenner Group (TBG) was appointed CEO, with Weston Rose of TBG to serve as president and Mark Thompson of TBG to serve as chief financial officer of the company during the continued restructuring.

• **Allon Therapeutics Inc.**, of Vancouver, British Columbia, regarding the proposal made by the company to its creditors pursuant to the Bankruptcy and Insolvency Act in Canada, said it has been advised that Deloitte & Touche Inc., as proposal trustee, has received an unsolicited offer from a third party. The company said Deloitte is investigating the matter and will provide updates to creditors as or when more information becomes available.

• **AMAG Pharmaceuticals Inc.**, of Lexington, Mass., said its European commercial partner, **Takeda Pharmaceutical Co. Ltd.**, of Tokyo, submitted a type-II variation to the European Medicines Agency (EMA) for Rienso (ferumoxytol). The submission requests EMA approval to expand the indication for ferumoxytol beyond the current indication for the treatment of iron deficiency anemia (IDA) in adult patients with chronic kidney disease to include all adult patients with IDA who have a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used.

• **Cardium Therapeutics Inc.**, of San Diego, held its annual meeting of stockholders and temporarily adjourned the meeting to allow additional time for stockholders to vote on two remaining issues related to a proposed reverse stock split and a charter amendment, which were favored by a majority of shares voted but which also require a majority of all outstanding shares, including unvoted shares. Of the votes that were cast before the meeting, about 61 percent voted in favor of the reverse stock split and about 66 percent voted in favor of the increase in the number of authorized shares. However, both proposals also require the affirmative vote of a majority of the issued and outstanding shares of Cardium's common stock, which includes more than 38 million shares that remain unvoted. The adjournment will allow for additional stockholders to vote on the proposals.

Stock Movers

6/7/13

Company	Stock Change	
Nasdaq Biotechnology	+$40.28	+2.20%
Cynapsus Therapeutics Inc.	-$0.07	-14.74%
NewLink Genetics Corp.	+$1.59	+9.00%
SkyePharma plc	+$2.75	+5.91%

(Biotechs showing significant stock changes Friday)

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Cyber Attacks

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unit of the Chinese military – which it identified as APT1 – as a main driver of hacking attacks and tracked the group's operations to a building in Shanghai's Pudong district.

The increased activity against biotechnology firms coincided with the inclusion of pharmaceuticals and health care as strategic growth industries in China's 12th Five Year Plan (FYP), that covers 2011-2015.

"We believe that organizations in all industries related to China's strategic priorities are potential targets of APT1's comprehensive cyber espionage campaign," Mandiant reported. "Our observations confirm that APT1 has targeted at least four of the seven strategic emerging industries."

Access to biopharma company networks would open up to the Chinese hackers drug trial information, chemical formulas and confidential data for all drugs sold in the U.S. market.

Typical attacks take the form of malware that comes in through e-mail attachments. Another approach is for hackers to infiltrate the networks of service providers and use them to attack target companies.

Chinese hackers have taken as much as 6.5 terabytes of information from a single company over a 10-month period, though it was not publically disclosed which company.

To date, however, it is difficult to say how the data have been used, and Mandiant stops short of explaining. Nor is it clear who may ultimately benefit or whether any biotechnology firms in China – even state-owned ones – have profited. Mandiant suggested a way has been found to commercialize the data to justify the size of the program, which likely employs hundreds of people and makes use of at least 1,000 servers, but there is no clear evidence.

"We judge that cyber espionage is one of the means employed by the PRC to meet the larger economic and social goals identified in the 12th FYP," Galante noted. "Beijing employs a variety of legitimate methods to fulfill this agenda but also uses computer network operations to steal global pharma corporations' IP. The PRC likely intends to use stolen IP to bolster its domestic pharmaceutical market."

The issue of hacking has been on the table in U.S.-China relations for several years. In November 2011, a combined report by 14 U.S. intelligence agencies named China as the main source of hacking threats in the world. The Chinese Ministry of Foreign Affairs has said on numerous occasions that it is, in fact, the real victim of U.S. attacks and that China "oppose(s) hacking attacks of any form."

China's Ministry of Foreign Affairs spokesperson, Hong

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BeiGene

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AstraZeneca plc for Shanghai-based Hutchison MediPharma Ltd.'s c-Met inhibitor anticancer candidate volitinib (HMPL-504) in 2011. (See *BioWorld Today*, Dec. 28, 2011.)

BeiGene, of Beijing, expects to start clinical development in China by next year for BeiGene-283.

For the deal, the companies announced there would be an undisclosed up-front payment to BeiGene, plus it would be eligible to receive further payments of up to $233 million for achievement of clinical development and potential commercial milestones in China and rest of the world and up to double-digit royalties on next sales.

BeiGene, less than 3 years old, will develop and commercialize BeiGene-283 in China, and Merck will develop and commercialize BeiGene-283 for the rest of the world.

In addition to possibly being one of the first novel molecules licensed out of China to a big pharma, the deal is significant on two counts.

First, the preclinical development was fast: less than 2.5 years from the beginning of bench science, BeiGene CEO John V. Oyler told *BioWorld Today*. Preclinical development can easily take up to five years. He said that stunning accomplishment lies with a highly talented team of 160 staff in China backed by a world-class team of international scientific advisors.

Second, it marks continued intense interest in BRAF inhibitor drug development. Last week, the FDA announced approval of only the second BRAF inhibitor, Tafinlar (dabrafenib, GlaxoSmithKline plc) as a single-agent oral treatment for unresectable melanoma or metastatic melanoma in adult patients with BRAF V600E mutation as detected by an FDA-approved test. The first BRAF inhibitor was Zelboraf (vemurafenib, Daiichi Sankyo Co. Ltd. and Roche AG) in 2011. (See *BioWorld Today*, Aug. 18, 2011.)

Those drugs are characterized by dramatic clearing of tumors for those who respond, but often the cancer comes back after a several months.

At the time of Zelboraf's approval, Roche trumpeted that its BRAF inhibitor was the first and only personalized medicine shown to help people with BRAF V600E mutation-positive metastatic melanoma to live longer.

What makes the BeiGene-283 especially intriguing is the concept that it appears to be a dual inhibitor, hitting BRAF and EGFR.

With that profile, comes the promise that it may be able to do what the first generation of BRAF inhibitors could not – treat colon cancer with the same BRAF mutation that it so effectively targets in melanoma.

Researchers from the Center for Biomedical Genetics, the Netherlands Cancer Institute, investigated what was causing very limited response to Zelboraf in colon cancer patients with the same BRAF mutation in a Jan. 26, 2012, *Nature* article: "Mechanistically, we find that BRAF(V600E) inhibition causes a rapid feedback activation of EGFR, which supports continued proliferation in the presence of BRAF [V600E] inhibition [in colon cancer cells]. Melanoma cells express low levels of EGFR and are therefore not subject to this feedback activation."

"Our data suggest that BRAF(V600E) mutant colon cancers [approximately 8-10 percent of all colon cancers], for which there are currently no targeted treatment options available, might benefit from combination therapy consisting of BRAF and EGFR inhibitors," the researchers noted. ■

Cyber Attacks

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Lei, said on June 4 that China and the U.S. have agreed to set up a cyber-working group under the China-U.S. Strategic Security Dialogue framework.

"China stands ready to engage in constructive dialogue with the U.S. on the issue of cyber security based on mutual respect and mutual trust," Lei said during a press conference. "Both sides have agreed to establish a cyber-working group within the framework of China-U.S. Strategic Security Dialogue. We hope that both sides could take an even-tempered and level-headed approach to the issue, build up understanding and consensus and enhance cooperation through dialogue and communication so as to jointly build a peaceful, secure, open and cooperative cyberspace."

Cyber security and IP were at the top of the agenda during meetings between President Xi Jinping and President Barack Obama in Palm Springs, Calif. last week. ■

Other News To Note

• **ImmunoCellular Therapeutics Ltd.**, of Los Angeles, said that a data monitoring committee has completed an interim analysis of its Phase II trial of ICT-107, a vaccine for glioblastoma, and recommended continuation of the trial. The trial has enrolled 124 patients at 25 sites in the U.S. The primary endpoint of the trial is overall survival. Secondary endpoints include progression-free survival, immune response and safety.

• **Regen BioPharma**, of San Diego, a wholly owned subsidiary of Bio-Matrix Scientific Group Inc., submitted responses to the FDA's comments regarding its investigational new drug application for HemaXellerate, for immune suppressant-resistant aplastic anemia. It provided new data showing efficacy of HemaXellerate for accelerating stem cell recovery after chemotherapeutic injury.

• **Royalty Pharma**, of New York, increased its hostile bid to acquire **Elan Corp. plc**, of Dublin, Ireland, offering $13 per share plus a contingent value right of up to $2.50 per share, for a potential value of $8 billion.

Financings Roundup

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based biotech reached out to angel groups. Existing investors Cherrystone Angels and Golden Seeds led the round, with participating investments from new Ariel Southeast Angel Partners and Tech Coast Angels and a host of existing angel investors – Beacon Angels, Boston Harbor Angels, Launchpad Venture Group, Mass Medical Angels, North Country Angels, the Beta Fund, Granite State, the Keiretsu Forum and Maine Angels.

All told, Avaxia has support from 12 angel groups, which founder and CEO Barbara Fox called a "wonderful and stable funding base."

Those groups, along with individual investors, "really stepped in to fill the gap that's been left by the relatively small number of venture firms investing in early stage development," she told *BioWorld Today*.

Also joining the round was AbbVie Inc. The big pharma's participation is equity only; it's not associated with any rights or options, so Avaxia is free to continue the partnering discussions launched at this year's BIO International Convention in Chicago. (See *BioWorld Today*, April 29, 2013.)

But AbbVie will get a seat on Avaxia's board – David Donabedian, managing director of AbbVie Biotech Ventures Inc., joined as part of the financing – adding strategic help from one of the leading firms in the inflammatory bowel disease (IBD) space, Fox said.

AbbVie's expertise in gastroenterology will be a "real asset to the development" of AVX-470, she added.

For its part, Chicago-based AbbVie, which was spun out of Abbott earlier this year to focus on its biopharmaceutical pipeline, leading with Humira, has been working to build up its pipeline in the gastrointestinal disease space. In May, it inked an extension to its deal with Galapagos NV to extend the clinical development of oral JAK1 inhibitor GLPG0543 into Crohn's disease. A Phase IIa/IIb study is set to start by early 2014 in 180 Crohn's patients, with data expected in the second quarter of 2015.

Also last month, AbbVie shelled out $70 million up front for an option to acquire a celiac disease drug from Alvine Pharmaceuticals Inc. The big pharma will be able to exercise its option upon the conclusion of Phase IIb testing of ALV003, a two-enzyme combination candidate designed to degrade gluten. (See *BioWorld Today*, May 15, 2013.)

According to Avaxia, IBD refers to related but different diseases: ulcerative colitis (UC), which affects the colon, and Crohn's disease, which affects the small intestine. Avaxia chose to test AVX-470 in UC first, though the drug has "real potential" in Crohn's disease, a space the firm intends to explore in the "near future," Fox said.

Avaxia launched the ongoing Phase Ib trial in February and has just completed the first dosing cohort. The study is designed to test the safety, tolerability, pharmacokinetics and pharmacodynamics of ascending doses in patients with UC. At least 24 patients expected to be enrolled, comprising three dose groups, with six patients in each group receiving AVX-470 and two receiving placebo, for a 28-day treatment period. Exploratory endpoints in the study are looking for clinical efficacy and inflammation biomarkers.

Assuming the study continues as planned, Fox said the company hopes to present data at the 2014 J.P. Morgan Healthcare Conference in January. The latest fundraising should get Avaxia through that trial "with a little bit of breathing room at the end," though the firm will need to look for additional investment – either through a financing round or a partnership – next year.

AVX-470 emerged from Avaxia's technology platform, which is designed to create antibodies isolated from the early milk of immunized cows. In addition to safety, the advantage of those antibodies is that they are designed to specifically target antigens in the gastrointestinal lumen such as sugar transporter and receptors of the small intestine.

Currently marketed anti-TNF drugs such as Humira – also Johnson & Johnson's Remicade (infliximab) and UCB SA's Cimzia (certolizumab) – represent more than half of the $4.5 billion-plus IBD market. But those injectable biologics carry some long-term risk. By targeting oral AVX-470 specifically to the gut, Avaxia has said its drug should avoid the systemic exposure and reduce the systemic immunosuppression that usually results from the injectable anti-TNF antibodies.

In addition to its work in IBD, the firm also has a contract via the Biomedical Advanced Research and Development Authority for a program using its oral anti-TNF drug in acute radiation syndrome. Approval for radiation use requires only animal testing and so far, Fox noted, "we've seen some very promising early stage data."

While mostly supporting the ongoing Phase Ib study, proceeds from the latest round also will be used in starting up drug manufacturing for Phase II studies and other pipeline development, as well as for general corporate purposes.

In other financings news:

• **Array BioPharma Inc.**, of Boulder, Colo., said underwriters in its previously announced offering of 3 percent convertible senior notes due 2020 exercised in full their option to purchase $17.25 million more in aggregate principal amount of notes. Including the full exercise of the option, Array will issue a total of $132.25 million in aggregate principal amount, for proceeds of $128 million after deducting the underwriting discount and estimated offering expenses payable by Array. The company expects to use the $92.6 million of the net proceeds to repay its outstanding secured indebtedness, with the remaining proceeds expected to be used for general corporate purposes.

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Antibody

Continued from page 1

issue of *Cell*, the researchers focused on one particular region of the antibody – the complementarity-determining region 3 (CDR3). Complementarity-determining regions are the business end of antibodies, which interact directly with the target antigens. In humans, the CDR3 region is typically 8 to 16 amino acids long. Cows, on the other hand, have CDR3 regions that are not only longer by a few amino acids on the average: About 10 percent of their antibodies have CDR3 regions that can be more than 50 amino acids in length.

The team's interest in those antibodies, corresponding author Vaughn Smider told *BioWorld Today*, began because there are also rare human antibodies with a long CDR3. And such antibodies appear to be good at neutralizing otherwise hard-to-fight pathogens; one human antibody has been isolated that neutralizes HIV via a very long CDR3 region.

The team generated a crystal structure of such long antibodies, and found that the CDR3 region had a very unusual structure. "Typically, antibodies have a flat binding surface," Smider explained. For antibodies with ultralong CDR3 sequences, "that CDR3 is a long protruding structure. . . . It almost looks like a small mushroom."

Smider and his team named it the "stalk and knob" structure, and found that it contains a large number of cysteines, an amino acid that can form a specific type of chemical bond with other cysteines. Those bonds give the stalk-and-knob shape both stability and diversity.

Further experiments showed that the genes coding for the knob segments of the long CDR3 regions were highly likely to develop point mutations that added or removed cysteines. Such changed cysteine patterns in the CDR3 would lead to the formation of different cysteine-cysteine bonds – which would change the shape of the knob and so increase the diversity of the cow's antibody repertoire.

Such diversity is important for all species to keep up with their bacterial and viral enemies. Cows may need an especially diverse repertoire of antibodies because of their digestive system, which consists of four stomachs that ferment their food, providing multiple opportunities for pathogens to thrive.

Smider is on the faculty at the Scripps Research Institute. He is also the founder and president of San Diego biotechnology firm Fabrus Inc., whose goal is to expand the target space for antibodies. Fabrus is generating libraries of the long antibodies and plans to explore them for oncology and pain indications.

The knobs, it turns out, are about the same size and shape as certain animal toxins that bind to ion channels – a class of drug targets that human antibodies don't bind to particularly well. They also have similarities to chemokines, which may mean they have potential for expanding the reach of antibodies into another class of drug targets: G-protein coupled receptors or GPCRs.

Taking advantage of interspecies diversity, of course, can also have its pitfalls. Specifically, antibodies from other species – at this point, mainly mice – can lead to immune reactions. Smider acknowledged that "the cow antibody needs to be humanized," and that such humanization is not fully possible precisely because the stalk and knob structure is not usually found in human antibodies. But antibody's scaffold can be humanized, a task that the team is making progress on.

Scientifically, the findings showed that point mutations are one way to generate antibody diversity. They also suggested that antibody diversity may be broad not just within individuals, but also across species.

Camels and llamas, as well as sharks, have antibodies that are structurally unusual. Belgian biotech firm Ablynx NV's nanobodies are modeled on camelid antibodies, which lack light chains.

Species differences between antibodies are still more of the exception than the rule. But the findings are another example that looking across species may yield still other useful antibody shapes. "The more people look," Smider said, "the more things they find." ■

Financings Roundup

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• **BioTime Inc.**, of Alameda, Calif., said it closed its equity financing and received gross proceeds of about $9.1 million. The funds will be used for working capital and other general corporate purposes, and BioTime said it may invest a portion in one or more of its subsidiaries, including funding the expansion of LifeMap Sciences Inc.'s product development and research programs. ■

Clinic Roundup

• **Arena Pharmaceuticals Inc.**, of San Diego, said that Belviq (lorcaserin) will be available in the U.S. by prescription beginning June 11. **Eisai Inc.**, of Woodcliff Lake, N.J., is responsible for marketing and distribution of the drug. Belviq is approved for chronic weight management in adults with a body mass index of 30 or more, in addition to a reduced calorie diet and increased physical activity.

• **Bio-Path Holdings Inc.**, of Houston, completed the fifth dose cohort in a Phase I trial of BP-100-1.01, a candidate for blood cancers, including acute myeloid leukemia, chronic myelogenous leukemia, acute lymphoblastic leukemia and myelodysplastic syndrome. The three patients in the cohort completed the 28-day treatment cycle at 60 mg/m2 twice a week. Early results suggested the drug is well tolerated.

Partnerships

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Although pressure from those patients and from the Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) Association of America helped to convince the FDA to organize a public workshop in April to discuss strategies to improve regulatory guidance for the disorder, individuals with CFS may benefit from a separate effort to find new indications for drugs that failed to demonstrate efficacy in their initial targets. (See *BioWorld Today*, March 14, 2013, and May 22, 2013.)

CFIDS collaborated with Biovista Inc., using its clinical outcomes search space, or COSS, technology, to identify two candidates for CFS treatment that are being readied for proof-of-concept trials. The candidates moved to an FDA pre-investigational new drug (IND) meeting, scheduled for the third quarter, less than a year from the project's start, according to Aris Persidis, Biovista's president.

In contrast, the typical timeline to advance a compound through drug discovery and preclinical studies prior to IND filing is three to five years, according to data from the Pharmaceutical Research and Manufacturers of America. And that schedule doesn't count basic research and screening.

"To be able to have enough of an argument that the FDA will grant you a pre-IND within a 12-month period is very, very exciting," Persidis told *BioWorld Today*.

"There is a big gap in the pipeline that moves basic laboratory research into safe and effective treatments," observed Kimberly McCleary, president and CEO of CFIDS. "Without a bridge to bring discoveries to the clinic, laboratory research rarely becomes more than a paper."

"We understand the CFS knowledge base and know how to fill this gap," added Suzanne Vernon, scientific director of CFIDS. "Biovista recognized the opportunity for discovery."

COSS generates hypotheses about possible clinical outcomes and acquires data from multiple sources, including experiments, interaction and expression databases, reported outcomes, patents and scientific literature.

The tool then goes far beyond data mining, developing unique and standardized data profiles "for every drug, every disease, every adverse event and every molecular target known to modern medicine," Persidis said.

The profiles are compared and ranked to identify the best matches for a given target in a variety of uses, such as finding new drugs for a certain disease or patient subpopulation, suggesting effective drug combinations for a particular condition or discovering comorbidities among patient populations that could increase the risk of adverse events.

COSS "allows us to answer the most important question in translational medicine," Persidis said, "which is 'How can I make sense of the data I have and translate it into something that will affect the patient at the point of care?'"

'Making a Better Bet'

CFS isn't the only indication where COSS is showing mettle. Charlottesville, Va.-based Biovista has collaborations with Pfizer Inc., of New York, and Novartis AG, of Basel, Switzerland, as well as the FDA's Office of Clinical Pharmacology. (See *BioWorld Today*, Nov. 10, 2010, and *BioWorld Insight*, Nov. 29, 2010.)

In March, Cambridge, Mass.-based DART Therapeutics Inc. inked an agreement with Biovista to evaluate and rank molecules identified by COSS, providing DART with a short list of de-risked candidates that could be in-licensed.

Like CFIDS, DART is allied with an energized patient population – in its case, the Duchenne's muscular dystrophy (DMD) community, which aggressively searches the scientific literature seeking therapeutic assets that could be repurposed for DMD, explained Gene Williams, DART's executive chairman and CEO. By partnering with Biovista, DART hopes to find the most promising assets.

"We're very happy with where we've gotten so far," Williams told *BioWorld Today*.

After running COSS for nearly 15 years, Biovista "has developed a very sophisticated tool for generating hypotheses," he added. Although the methodology is essentially the same as a scientist might use to "connect the dots" between a drug's mechanism of action and a disease target before conducting confirmatory research, "COSS does this in a very comprehensive and efficient way."

DART discovered previously unidentified leads in its first COSS run. "More than half of them look extremely interesting," Williams said.

Unmet medical need persists, in part, because animal models are poorly predictive, he pointed out.

"If you have the sophisticated biologic hypothesis that COSS offers and you confirm that with an animal model, you're making a better bet," he said.

Cempra Inc., of Chapel Hill, N.C., forged a similar alliance with Biovista in 2008 to identify and profile adverse event associations for members of the macrolide drug class. At the time, the company was still in preclinical studies and had limited animal toxicology data on lead compound solithromycin (CEM-101), a first-in-class fluoroketolide antibiotic candidate, recalled Prabhavathi Fernandes, Cempra's president and CEO.

The company ran the COSS technology on solithromycin, an analog of telithromycin that does not contain a pyridine in the side chain of the molecule. COSS confirmed that solithromycin was not burdened by the toxicity profile of telithromycin.

"That was positive for us," Fernandes told *BioWorld Today*. "We moved forward, and we have since shown that solithromycin is superior, without the toxicity of telithromycin."

Although Cempra likely would have reached the

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Partnerships

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same conclusion without COSS, "it did provide us with reassurance," Fernandes said. The finding also helped the company to focus its research and resources. "If the COSS technology had suggested the compound might be toxic, like telithromycin, we might have been a little more worried and looked at some other compounds," she admitted.

Fernandes also praised the technology's ability to identify new potential pathways for existing or failed drugs. "That's going to be the big use of this technology in the future," she predicted.

Biovista has reached the same conclusion. Although the company has its own preclinical drug pipeline, it's beginning to place some of those candidates into virtual newcos while keeping the COSS platform as its star attraction – a canny strategy should its future include a venture financing or public offering.

Because COSS generates revenues from partners, either on a fee-for-service basis or in up-front and milestone payments, Biovista can fund early stage development of drug candidates after their vetting by COSS. The company is currently developing the first two newcos, which could eventually seek their own partners, Persidis said. ■

Clinic Roundup

• **Esperion Therapeutics Inc.**, of Plymouth, Mich., reported top-line results from a Phase IIa trial of ETC-1002 for hypercholesterolemia in patients with a history of intolerance to two or more statins. The study met its primary endpoint of lowering LDL-C, which it did by an average of 32 percent. The drug was well tolerated as well. The company plans to begin a Phase IIb study by the end of 2013.

• The Angeles Clinic and Research Institute presented results for MPDL3280A, a cancer candidate by **Genentech Inc.**, of South San Francisco. In the Phase I study, of 140 evaluable patients treated with the drug, 29 (21 percent) showed tumor shrinkage by RECIST criteria, with the highest responses in patients with non-small-cell lung cancer and melanoma. MPDL3280A is an antibody designed to target and block the function of programmed death ligand 1 (PD-L1), which is often overexpressed on the surface of cancer cells.

• **Puma Biotechnology Inc.**, of Los Angeles, began a Phase III trial of PB272 (neratinib) for HER2-positive metastatic breast cancer patients who have failed two or more previous treatments. Participants with third-line HER2-positive metastatic breast cancer will receive PB272 Xeloda or Tykerb plus Xeloda. The primary endpoints of the trial will be progression-free survival and overall survival.

Pharma: Clinic Roundup

• **Pfizer Inc.**, of New York, began a Phase I trial of PF-06410293 (adalimumab), its biosimilar version of Humira. The trial will enroll about 210 subjects. Its primary objective will be measuring pharmacokinetic values, with secondary objectives including incidence of anti-adalimumab antibodies and neutralizing antibodies, time to maximum serum concentration, systemic clearance and serum decay half-life.

BENCH PRESS

BIOWORLD LOOKS AT TRANSLATIONAL MEDICINE

MONDAY, JUNE 10, 2013

Bombs, Brains and Stem Cells

Researchers from the **Swedish Karolinska Institutet** have used the consequences of nuclear testing in the 1960s to estimate the rate at which new neurons are born in adult human brains. Such nuclear testing raised the level of carbon-14 (as opposed to the regular carbon-12) in the atmosphere, and since it was banned in 1963 those carbon levels have been declining at a known rate. The authors used that knowledge to essentially carbon-date human neurons, and they were able to show that several hundred neurons are born daily in the hippocampus, a brain region that plays a role in learning and memory as well as disorders like depression. The authors concluded that the rates of neuronal renewal are similar in humans and mice, which validates the use of mouse models to look at processes where neurogenesis plays a role. The findings appeared in the June 6, 2013, issue of *Cell*.

Huntington's and Brains and Stem Cells

For those cases where endogenous stem cells don't produce what is needed, meanwhile, researchers from the **University of Rochester Medical Center** have discovered a way to coax endogenous neural stem cells into producing medium spiny projection neurons, a type of neuron that is among those lost in Huntington's disease. The authors used gene therapy to deliver two genes for growth factors directly into the brains of transgenic mice that are transgenic for one part of mutant huntingtin and so develop the equivalent of Huntington's disease. Such animals did develop Huntington's disease, but their motor function deteriorated more slowly. The animals also lived almost two months longer than untreated controls, which worked out to a life span increase of more than 30 percent. The authors also showed that treating monkeys with the same viral vector also increased the formation of new neurons in their brains. The authors cautioned that their findings will need to be validated in animal models with full-length mutant huntingtin, but they also concluded that "we believe that our data suggest the feasibility of induced striatal neuronal addition as a viable therapeutic strategy for [Huntington's disease]." Their findings appeared in the June 6, 2013, issue of *Cell Stem Cell*.

Stem Cell Surprise in Myeloproliferation

Scientists from the British **University of Cambridge** have shown that a driver mutation for myeloproliferative neoplasms has an unexpected effect on blood stem cells: It reduces their capacity for self-renewal. The JAK2V617F mutation is a driver of such disorders, which are characterized by overproduction of one or more types of blood cell and can progress to outright leukemia. In their work, the authors used single-cell analysis of cells with an inducible JAK2V617F mutation to look quantitatively at the cell fates of cells descended from a stem cell with that mutation, and found that it left blood-forming stem cells less able to self-renew and more likely to differentiate. In progenitor cells, on the other hand, the mutation had the opposite effect. Cells were more likely to proliferate. The authors said the stem cell deficit they observed was "relatively subtle and [required] serial transplantation assays to be revealed; acquisition of JAK2V617F would therefore not be predicted to result in clonal extinction during the lifespan of a patient," which could explain why a mutation that impairs stem cell function could lead to a surfeit of cells. Their findings appeared in the June 4, 2013, issue of *PLoS Biology*.

Stop Trans-Translation, Bacteria Sputters

Researchers from **Pennsylvania State University** validated a pathway that is present in every bacterial species sequenced to date, but absent in animals, as a drug discovery target for antibiotics. The so-called trans-translation pathway is a way for bacteria to end translation reactions; it consists of several different proteins that work together to remove proteins of the bacterial ribosome from the RNA when there is no stop codon. Before their removal, such proteins must be tagged. In their work, the authors showed that inhibiting such tagging leave bacteria unable to release their freshly translated proteins, which ultimately killed several different bacterial species. The authors concluded that inhibiting the trans-translation "target could play a key role in combating strains of pathogenic bacteria that are resistant to existing antibiotics." Their work appeared in the June 3, 2013, advance online issue of the *Proceedings of the National Academy of Sciences*.

Shutting Off Immunity via Nanoparticles . . .

A team from the **Scripps Research Institute** has found a way to kill antibody-producing B cells that react to specific antigens, potentially paving the way toward

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getting rid of unwanted immune responses without wholesale repression of the immune system. Currently, there is no way to affect B cells according to which antigen they target, and so dampening the immune system comes with the tradeoff of increased vulnerability to infections. For their studies, the authors made nanoparticles that had both specific antigens and inhibitory B cells on their surfaces. They tested their nanoparticles in mice with hemophilia to see whether they could prevent the development of an immune response to recombinant Factor VIII, which is a frequent problem in hemophiliac individuals. They were able to shut off such a response, "suggesting that [these nanoparticles] may provide the basis of a strategy for preventing and eliminating harmful antibody responses in humans." The study appeared in the June 3, 2013, advance online edition of the *Journal of Clinical Investigation*.

. . . Or Blood Cells

Researchers from the Swiss **University Hospital Zurich** and the **Center for Molecular Neurobiology** in Hamburg, Germany, have developed a different method for specifically shutting off unwanted immune responses, which they tested in a Phase I trial as well as in animal models. In that case, the authors coupled autoantigens to blood cells and injected them into mice with the equivalent of multiple sclerosis. Blood cells die by the billions every day in circulation, and the immune system has evolved specific mechanisms to recognize the proteins they release during death as harmless. By coupling antigens that are frequent targets of the immune system in multiple sclerosis, the authors were able to induce immune tolerance to those antigens. They performed a Phase I trial in seven patients and found that the treatment was well tolerated, and patients receiving the higher dose showed reduced autoreactive T-cell counts after treatment. The work appeared in the June 6, 2013, issue of *Science Translational Medicine*.

New Insights into Deadly Flu Strains

A team from the **Massachusetts Institute of Technology** looked at how highly lethal flu viral strains might gain the ability to spread easily between humans. The H7N9 influenza strain has been causing infrequent infections in humans and has had a high lethality rate when it does, but so far appears unable to spread easily between humans. The MIT team found that a single amino acid change might make the strain bind in the upper respiratory tract of humans, rather than the lower respiratory tract, which would be expected to make it more easily transmissible. H5N1 virus, on the other hand, did not switch into easy transmissibility when the authors engineered molecular changes into it that have led to the easy transmissibility of other flu strains. The authors said their studies "can be used to monitor the emergence of strains having human-to-human transmission potential," and have implications for both surveillance and vaccine development. They published their results in two separate papers in the June 6, 2013, issue of *Cell*.

Post-Exposure PTSD Prevention Possible?

Scientists from **Emory University** have shown that opioid receptor signaling is involved in post-traumatic stress disorder (PTSD). The authors identified the specific receptor by exposing animals to stress and then looking at differences in gene expression patterns between animals that developed PTSD-like symptoms and those that did not. They found that animals that were vulnerable to stress had lower levels of one type of opioid receptor, the NOP-R receptor. Drugs activating that receptor could prevent the formation of PTSD when given either before or directly after the animals were traumatized by severe stress. The authors also looked at genetic variants of the receptor in humans and found that a low-activity variant correlated with a self-reported history of childhood trauma, the development of PTSD symptoms after a traumatic event, and brain activity and connectivity that is associated with fear-based learning. The findings may point to new ways to prevent the development of PTSD after a traumatic event. Their work appeared in the June 6, 2013, issue of *Science Translational Medicine*.

Misfolded Proteins Subject to Peer Pressure

Scientists from the **University of Michigan** have gained new insights into how mutations that lead to misfolded proteins translate into disease. There are several so-called conformational diseases, where such misfolding due to a mutated gene blocks proteins from being exported into the cell after they are synthesized in the endoplasmic reticulum. Such mutations often are dominant, that is, they lead to disease even if only one of the two copies is mutated. The authors studied two specific mutations that can lead to disease, and found that in each case, when wild-type and mutant proteins bound to each other, the wild-type protein could help the mutant escape the endoplasmic reticulum, but the mutant also could retain the wild-type. Which outcome was more likely depended on the relative levels of mutant to wild-type protein, with higher levels of wild-type protein increasing the likelihood that mutants would be exported as well. The findings, which support the idea that one way to treat disorders of protein folding is to try to affect the ratio of wild type to mutant protein production within cells, were published in the June 3, 2013, advance online edition of the *Journal of Clinical Investigation*.

– *Anette Breindl, Science Editor*