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## AMERICAN ACADEMY OF NEUROLOGY 67TH ANNUAL MEETING

### Progress coming in amyotrophic lateral sclerosis, but rigorous studies needed

By Marie Powers, News Editor

The community of individuals living with amyotrophic lateral sclerosis (ALS), or Lou Gehrig's disease, has endured many false hopes for promising therapies and is still waiting for the first disease-modifying drug. Nevertheless, "we have made huge progress in the last decade in ALS," Merit Cudkowicz, professor of neurology at Harvard Medical School and chief of the neurology service and director of the MDA ALS Clinic at Massachusetts General Hospital, told participants in an integrated neuroscience session on ALS at the American Academy of Neurology (AAN) 67th

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## IN (WHAT ELSE?) IMMUNOTHERAPY

### Potenza credenza stocked as cancer-zealous Astellas nails down another deal

By Randy Osborne, Staff Writer

Having banked \$38 million in a series A round late last year, cancer immunotherapy firm [Potenza Therapeutics Inc.](#) is "in good shape in terms of financing," thanks also to an undisclosed amount of new money from a deal with [Astellas Pharma Inc.](#), CEO

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## IN THE CLINIC

### Biontech gives scientific rationale for personalized RNA cancer vaccines

By Cormac Sheridan, Staff Writer

DUBLIN – Has the era of truly personalized cancer immunotherapy begun? [Biontech AG](#) certainly thinks so – and the German biotech firm has published in vivo proof-of-concept data

[See Biontech, page 5](#)

## REGULATORY

### U.S. dearth of MCMs like 'an army without bullets'

By Mari Serebrov, Regulatory Editor

With the consequences of the delayed response to the Ebola crisis still fresh on their minds, members of a House subcommittee Wednesday stressed the need to step up U.S. preparedness for bioterrorism attacks.

At the heart of that effort should be a

[See MCMs, page 6](#)

## FINANCINGS

## T CELLS AND BEYOND

### Jounce bounces on immunotherapy fervor; adds \$56M in series B

By Jennifer Boggs, Managing Editor

Transitioning from discovery stage to human proof of concept is the next goal for cancer immunotherapy firm [Jounce Therapeutics Inc.](#), which added \$56

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## PARTNERSHIPS IN CLINICAL TRIALS

### #PCTUS explores roles of China, India in global clinical development

By Karen Pihl-Carey, Staff Writer

BOSTON – Shorter timelines to market and larger patient pools serve as major incentives for companies to bring clinical development work to China and India, although regulatory and cultural

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## EARNINGS

### Amgen's Q1 earnings rise as it charges more, spends less on R&D

By Michael Fitzhugh, Staff Writer

Markups on [Amgen Inc.](#)'s best-selling drugs, [Enbrel](#) (etanercept) and [Neulasta](#) (pegfilgrastim), and downsized R&D spending helped the company boost first quarter net income by 51 percent

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**REGULATORY FRONT**

The **California Legislature** is expected to mark up a bill this week that, if passed, would require each manufacturer of a prescription drug offered in California that has a wholesale acquisition cost of \$10,000 or more annually or per treatment course to file an annual report detailing the total R&D, clinical trial, manufacturing, regulatory, patent, acquisition and marketing costs of the drug. The report, which would be publicly posted online, would have to include any R&D support the drugmaker received from a state or federal agency. The Pharmaceutical Cost Transparency Act also would require drugmakers to disclose an annual history of price increases for the drug, profits realized from the product and total amount of financial help provided through patient prescription assistance programs.

**Baxter International Inc.**, of Deerfield, Ill., filed a complaint with the U.S. International Trade Commission alleging that **Novo Nordisk A/S**, of Bagsvaerd, Denmark, violated the Tariff Act in importing certain recombinant Factor VIII products into the U.S. The complaint asks that the commission issue a limited exclusion order, cease and desist orders, and a bond on the infringing products during the 60-day review period. In a notice slated for publication in Thursday's *Federal Register*, the commission said it will accept comments on the complaint through May 1.

The U.S. House, by voice vote, passed the **Ensuring Patient Access and Effective Drug Enforcement Act, H.R. 471**. The bipartisan bill, which now goes to the Senate, combats prescription drug abuse by increasing collaboration between the Drug Enforcement Agency, prescription drug distributors and pharmacies while preserving patient access to necessary drugs. The legislation also directs the Department of Health and Human Services (HHS) to submit a report, within one year of enactment, on the impact law enforcement activities have on patient access.

**Medicare Part B drug expenditures** could have been reduced by \$251 million between the second quarter of 2013 and the third quarter of 2014 had infusion drugs used in conjunction with

**STOCK MOVERS 4/22/2015**

Company	Stock in \$	Change in %
Nasdaq Biotechnology	-\$11.12	-0.29%
Aldeyra Therapeutics Inc.	-\$1.45	-13.49%
Atara Biotherapeutics Inc.	+\$7.64	+13.61%
Celladon Corp.	-\$2.77	-16.93%
Biotechs showing significant stock changes Wednesday		

durable medical equipment (DME) been covered according to the payment structure used for other Part B drugs, the HHS Office of Inspector General (OIG) reported. The payment amounts for DME infusion drugs are set at 95 percent of the average wholesale prices that were in effect Oct. 1, 2003. But the payment amounts for most other Part B prescription drugs are set at 106 percent of the volume-weighted average sales prices (ASP), which are regularly updated. At least 42 percent of DME infusion drugs between 2013 and 2014 had Medicare payment amounts that were more than twice their estimated acquisition costs, according to the report. OIG recommended that the Centers for Medicare & Medicaid Services (CMS) either seek a legislative change requiring ASP-based payment for DME infusion drugs or include the drugs in the next round of its competitive bidding program. CMS responded that DME infusion drugs will not be included in competitive bidding until at least 2017.

The **Patient-Centered Outcomes Research Institute (PCORI)** this week approved more than \$120 million in awards to fund 34 patient-centered comparative-effectiveness research (CER) studies. The new awards include nearly \$58.5 million for five pragmatic clinical studies involving radiation therapy for breast cancer, fractures in older adults, and treatments for children with bipolar disorder and Crohn's disease. The other 29 awards will support studies comparing options for improving outcomes for conditions such as opioid addiction, arthritis, stroke, Parkinson's disease, leukemia, chronic kidney disease and child abuse. They also will explore ways to conduct more rigorous patient-centered CER and improve patients' access to care.

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## AAN

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annual meeting.

Researchers in the field have developed new ideas about what causes the disease and what pathways can be targeted for therapeutic approaches, and people with ALS are living longer, with an improved quality of life, Cudkowicz said. Two drugs are approved in the U.S. targeting symptomatic treatment. Rilutek (riluzole, Sanofi SA), which has been on the market for two decades, is designed to block glutamatergic neurotransmission in the central nervous system and prevent apoptosis of the motor neuron, although the beneficial effects are modest, typically prolonging life of an individual with ALS by only a few months. Nuedexta (dextromethorphan hydrobromide and quinidine sulfate, Avanir Pharmaceuticals Inc.), approved in 2010, is approved to treat pseudobulbar affect. (See *BioWorld Today*, Dec. 13, 1995, and Nov. 2, 2010.)

Those drugs are just the tip of the spear, with nearly two dozen others following behind. Among the candidates Cudkowicz cited were Gilenya (fingolimod, Novartis AG), approved to treat multiple sclerosis, the epilepsy drug retigabine (Potiga/Trobalt, Valeant Pharmaceuticals International Inc./Glaxosmithkline plc), and Actemra (tocilizumab, Genentech/Roche AG), approved to treat rheumatoid arthritis. London-based Glaxosmithkline also is advancing ozanezumab, an immunomodulator now in a phase II program, and Neuraltus Pharmaceuticals Inc., of Palo Alto, Calif., earlier this week reported the publication of phase II data showing positive trends in its candidate, NP001, for slowing ALS disease progression.

Also on the list was Nurown, from Brainstorm Cell Therapeutics Inc., of Hackensack, N.J., which disclosed data this week that included a piece-wise linear regression analysis of ALS patients who received the bone marrow-derived neurotrophic factor-producing mesenchymal stem cells in a phase IIa study and a prior phase I/II study. The data suggested a statistically significant improvement in the estimated rate of decline in forced vital capacity and a nearly significant improvement in the rate of ALS Functional Rating Score-Revised decline at six months post-treatment.

Benjamin Brooks, medical director, at Carolinas Neuromuscular/ALS-MDA Center and professor of neurology at the University of Wisconsin School of Medicine and Public Health, also presented detailed safety data during the ALS session from an ongoing phase II study of the Medicinova Inc. candidate, ibudilast (MN-166). The La Jolla, Calif.-based company reported this week that ibudilast raised no safety or tolerability concerns compared with placebo after three months of treatment, and the study is continuing as planned.

Cudkowicz admitted that the list of drug prospects is growing faster than her ability to track them. Still, “we’re really just at the beginning of learning” how to help ALS patients, she acknowledged.

Like many degenerative neurological diseases, the ALS space has been noteworthy for spectacular failures. In recent years, they included lead compound olesoxime from French biotech Trophos AS – a company acquired earlier this year by Roche AG, of Basel Switzerland – and dexpropampridone, developed by Cambridge, Mass.-based Biogen Inc. in partnership with Knopp Biosciences LLC, of Pittsburgh. (See *BioWorld Today*, Dec. 14, 2011, and Jan. 4, 2013.)

Another that was on the endangered list, tirasemtiv (formerly CK-2017357), a fast skeletal muscle troponin activator from Cytokinetics Inc., of South San Francisco, was given a second chance after a phase IIb failure with a reconfigured phase III trial that impressed analysts with a solid design. (See *BioWorld Today*, April 28, 2014, and Feb. 17, 2015.)

Studying the effect of drugs in ALS remains a tricky business, Cudkowicz said, due to the late stage of many patients at diagnosis, the enormous heterogeneity of the disease and the dearth of validated biomarkers. Those stumbling blocks make study design a challenge – especially studies that are powered sufficiently to predict success in pivotal trials.

Because of the tremendous clinical variability in ALS, “we can’t predict efficacy in small studies” that enroll a limited number of patients, Cudkowicz cautioned, because “we don’t know if there is also biological variability.”

Small, open-label phase II studies may enroll a disproportionate number of slow ALS progressors, which could cause them to make unsubstantiated efficacy claims, she suggested. Others might enroll disproportionate numbers of quick progressors, which could prompt them to mistakenly conclude that the study drug has no effect. Both extremes hurt the ALS field, according to Cudkowicz.

“If we put too much faith in such studies, we might be misled,” she said.

### **‘SPEND MORE TIME IN PHASE II’**

Although ALS researchers are improving the design of early stage studies as more is learned about potential targets, Cudkowicz suggested that “one lesson for field is to spend more time in phase II,” where researchers can take the time to select the appropriate dose and target.

Early trial design in ALS should focus on the intervention and restrict the lessons learned to the targeted biological action, tolerability and the relationship to dosage, she advised. Thoughtful trial design should address whether the study drug reaches the targeted tissue at a sufficient concentration and in a biologically active form. These studies also should inform whether the treatment acts as intended biologically, influences downstream biology or pharmacology and, if so, at what dosage and toxicity level, she added.

That’s precisely the beef the FDA appears to have with GM604, an AKT protein kinase stimulator from Genervon Biopharmaceuticals LLC that was another drug on the list of

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## Potenza

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Daniel Hicklin told *BioWorld Today*.

The Cambridge, Mass.-based firm will be advancing a portfolio of candidates that target immune checkpoint pathways, co-stimulatory signals, and regulatory T cells, with Tokyo-based Astellas holding an option to buy out Potenza if the collaboration goes well.

Under the terms, Potenza will lead drug discovery activities and hand over development prospects to Astellas, which will handle clinical development and commercialization. Financial terms were not detailed but include, along with the acquisition option, an equity investment, option fee, research funding and milestone payments.

“We’ll of course participate in strategy and work with them to do translational research, but it’s their responsibility to conduct the clinical trials,” Hicklin said. “We’re not giving out information on the exact timing [but] it’s obviously over several years, since we’re still in the preclinical stage.” Founded in 2014, Potenza takes its name from the Italian word meaning strength, as in strengthening the immune system to fight tumors. “We’ve been in stealth mode since the start of the company last March,” he said.

Potenza’s scientific advisory board includes researchers from the likes of Johns Hopkins University, Memorial Sloan-Kettering Cancer Center and Harvard Medical School. “We had a meeting

with our scientific founders about a year ago, and that’s where we laid out the vision and some of the concepts for the company,” Hicklin said. “We’ve been building upon that over the past year. Some of [the ideas] are coming out of our scientific founders’ labs and some have been generated within the company over the past year. Our approach is really to target a variety of complementary mechanisms that are involved in immunity.”

The firm “actually began discussions with Astellas quite early in building up Potenza, and they expressed interest in participating in some fashion with us” as the team and portfolio were assembled, Hicklin said, and “the culmination of those discussions is this R&D partnership.”

Astellas has been beefing up its oncology pipeline lately, hoping to add to the prostate-cancer therapy Xtandi (enzalutamide), approved in 2012 and co-marketed with Medivation Inc., of San Francisco. The drug was initially cleared as a second-line treatment and gained a first-line label last year. (See *BioWorld Today*, Sept. 4, 2012.)

Earlier this month, Astellas and the University of Texas MD Anderson Cancer Center disclosed an option agreement to research and develop a new treatment for patients with acute myeloid leukemia. The deal grants Astellas an option to first negotiate an exclusive, worldwide license at the end of phase Ib trials, with phase Ia and phase Ib studies to be conducted by MD Anderson. The agreement also includes up to \$26 million as an option premium and research and development funding.


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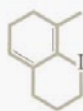


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## Biontech

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in the April 23, 2015, issue of *Nature* to back up its claims.

The Mainz-based company has obtained what it described as “potent tumor control and complete rejection of established aggressively growing tumors” in two murine cancer models, using RNA vaccines encoding 10 immunogenic neo-epitopes identified by surveying the mutational landscape – or mutanome – of each individual cancer.

A phase I study based on the same concept is already under way in 15 melanoma patients. “At the moment, seven patients have received treatment,” Biontech co-founder and CEO Ugur Sahin, who is lead author on the *Nature* paper, told *BioWorld Today*. “We will have completed treatment by the end of this year.”

Sahin, who also holds an academic post at the Johannes Gutenberg University, in Mainz, has been developing this approach for some time. His group published an influential study three years ago, in the March 1, 2012, issue of *Cancer Research*, which set out basic contours of the approach.

“We were the first group worldwide suggesting this approach, using next-generation sequencing and vaccination,” he said.

It involves whole-exome sequencing of tumor biopsies and samples taken from healthy tissue, to identify tumor-specific mutations. The company has developed a bioinformatics-based method for identifying the likely immunogenic mutations within a given cancer based on two parameters – their binding affinity for major histocompatibility complex (MHC) class II molecules and their level of expression in the tumor microenvironment, based on mRNA expression profiling.

“When we started this approach, most people were extremely skeptical,” Sahin said. But his stance has been vindicated by accumulating evidence from other groups, which links the presence of a pre-existing T-cell response to a likely response to checkpoint inhibitor blockade. “It is very clear that about 20 percent of patients respond,” Sahin said. “The question is what are the rules? Why do 80 percent of patients not respond and 20 percent do respond?”

The current paper contains two significant findings that challenge existing dogma on the immunogenicity of tumor mutations. It has generally been thought, Sahin said, that only about one in 200 cancer mutations is immunogenic, a frequency that would limit Biontech’s approach to a narrow set of cancers with a high frequency of mutations, such as melanoma or smoking-associated lung cancers.

“Our paper shows that the rate of immunogenicity is much higher,” Sahin said. His group estimated that about one in 20 mutations elicit an immune response, meaning that the approach could cover more than 75 percent of cancer types.

“The main reason for the underestimate is almost all researchers looked for spontaneous immune responses,” he said. Many may have been masked by tumor-induced immune suppression. “We asked questions about vaccine-relevant immunogenicity.”

The new research also shows that those tumor-associated mutations that are immunogenic generally drive a CD4 helper T-cell response, rather than a CD8 killer T-cell response. “If you take 10 immunogenic mutations, nine are recognized by CD4 T-cells – only one is recognized by CD8 T-cells,” Sahin said. The latter have generally received more attention up to now, he said. “Most tumors are infiltrated by both CD4 and CD8 cells but the number of CD8 cells is usually higher,” he said. However, this neglects the biological importance of CD4 T-cells as orchestrators of the immune response. “You cannot determine the relevance just by counting them.”

The CD4 T-cell response alters the tumor microenvironment, leading to CD8 T-cell infiltration, the elimination or reduction of immunosuppressive regulatory T-cells. The approach was successful in the B16F10 melanoma model, which is considered very aggressive, Sahin said. “Most checkpoint inhibitor approaches fail in this cell line.” It also worked in the CT26 model of colon cancer with lung metastasis, which usually results in death 20 days after inoculation.

Translating this approach into a clinical context is already under way – an interim data analysis will provide the first clues about whether it’s working. Optimizing the technology for scale-up is a work in progress, but developing individualized RNA-based vaccines is not the same challenge as delivering autologous cell therapies, Sahin said. Biontech only needs a sample from a standard cancer biopsy and a blood sample.

“We do not need to build a complex infrastructure at the study site,” he said.

Nor does the company need to treat every single vaccine as a single molecule, from a regulatory perspective. “We are not seeking approval for 100 molecules,” Sahin said. The company is also engaged in dialogue with regulators. Sahin, together with several other academic and industry researchers and German regulators, published a position paper – titled “The regulatory landscape for actively personalized cancer immunotherapies” – in the October 2013 issue of *Nature Biotechnology*, which set out a development strategy based on the existing regulatory framework. The approach is similar to that used in regulating cell therapy.

“You keep the process stable and do some sort of quality control on the product – that’s what we are doing,” he said.

Several others are developing personalized cancer vaccines based on slightly different approaches. For example, Beatriz Carreno, of Washington University in St. Louis, and colleagues, recently reported on the treatment of three advanced melanoma patients with an autologous dendritic cell vaccine, which had been exposed *ex vivo* to seven immunogenic peptides identified through cancer genomics. (See *BioWorld Today*, April 2, 2014.)

The *Nature* paper included co-authors from TRON Translational Oncology at the University Medical Center of Johannes Gutenberg University, the Research Center for Immunotherapy, in Mainz, and La Jolla Institute for Allergy and Immunology, in La Jolla, Calif. //

## MCMs

### [Continued from page 1](#)

buildup of the national stockpile of medical countermeasures (MCMs). Although the federal government has identified 15 biologic agents that could be used in such an attack, MCMs exist to counter only two or three of them, said Rep. Martha McSally (R-Ariz.), chairwoman of the House Homeland Security Committee's Emergency Preparedness subcommittee.

Former Sen. Jim Talent agreed, adding that not having MCMs is like having "an army without bullets." A national stockpile of MCMs that would address the most likely targets would force terrorists to work beyond their means to develop an agent for which there is no ready countermeasure, he said.

In addition to drugs and devices to counter a biologic attack, Charles Cairns, the interim dean of the University of Arizona College of Medicine Health Sciences Center, stressed the need for diagnostics that could rapidly identify biologic threats – be they naturally occurring diseases or acts of terrorism. The lack of locally available, real-time diagnostics hindered the Ebola response in the U.S., he asserted. There also was no information available to local hospitals about the therapies being used to combat Ebola. Another stockpile need is therapies developed for special populations. "We're not stockpiling as well as we should," Talent said.

Marisa Raphael, deputy commissioner of New York City's Office of Emergency Planning and Response, said local responders know they can't bank on the federal government in the first few hours of a disaster or emergency. Yet they are completely dependent on the federal government to provide MCMs from the stockpile. In New York, local distribution centers would be open before MCMs would be available.

If the national stockpile is going to grow and be more effective, the government must provide sufficient, consistent funding, advised Talent, a senior fellow at the American Enterprise Institute and the former vice chairman of the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism. More funding also is needed for the various agencies charged with supporting MCMs and responding in an emergency.

Several years ago, the commission gave the federal government an "F" in preparedness. "It's hard for me to believe that any link in this chain has gotten better," Talent said, citing budget restrictions aimed at lowering the deficit.

### **COORDINATION NEEDED**

Funding isn't the only challenge facing agencies like the Centers for Disease Control and Prevention, FDA, National Institutes of Health (NIH) and Biomedical Advanced Research and Development Authority (BARDA). Members of the subcommittee and witnesses at the hearing agreed there must be better coordination and information sharing among all federal agencies involved in emergency preparedness. Throughout the hearing, they bemoaned the lack of one clear lead in coordinating the country's Ebola response.

"We're almost stuck in place and time," McSally said, noting that recommendations made six to eight years ago to enhance the nation's preparedness have yet to be implemented. Even after the costly delay in responding to the Ebola crisis, there is still no one federal official in charge of such responses, she added.

Ranking Member Donald Payne (D-N.J.) called it a leadership vacuum that undermines every dollar spent on preparedness.

Aside from the overall lack of coordination across federal agencies, Talent called for more coordination among the NIH, FDA and BARDA, especially when it comes to a concerted focus on filling the stockpile.

Cairns added that the three agencies, as well as the rest of the federal government, need to prioritize the development of MCMs. At the FDA, that means facilitating the approval pathway, including finalizing and implementing the Animal Rule that would allow some MCMs to be approved based solely on animal testing. (See *BioWorld Today*, June 3, 2014.)

Another shortcoming among the agencies is a lack of communication with developers of MCMs. During the height of the Ebola crisis, it was difficult to interact with U.S. agencies on MCM development, Cairns said, noting greater interaction with officials in Canada and Europe. U.S. agencies need to understand the impact of MCMs and how they affect patients, Cairns added.

On the positive side, the FDA is making critical progress in assessing MCMs, he acknowledged, but it should specifically look at ones that can be used by emergency medical technicians and other first responders.

Talent agreed that the FDA is moving in the right direction in building its capacity to develop and approve MCMs more rapidly. But it must continue working to speed the process of "going from bug to drug" as quickly as possible, he said.

### **LOW PROBABILITY, HIGH CONSEQUENCE**

Calling a bioterrorist attack a "low probability but high consequence event," McSally stressed that such attacks from terrorist groups and "homegrown stray dogs" are an urgent and continuing threat. Dealing with a biological attack would be as equally challenging as a chemical threat, she said, with the added difficulty of diseases showing up weeks after the attack.

Bioterrorism also is graver than a nuclear threat, Talent said, pointing out that biologic agents can be as destructive as a nuclear attack and are more within the capabilities of terrorists with a background in the life sciences. Several areas in the world would provide terrorists the time and sanctuary needed to weaponize such agents.

"When you keep running risks, and the risks continue to grow, even gradually, the bullet is in the chamber," Talent said of the chance of a biologic attack.

The hearing, which McSally described as the first in a conversation on bioterrorism, came on the heels of a classified briefing the subcommittee received on the potential for biologic and chemical attacks in the U.S. //

## Jounce

### [Continued from page 1](#)

million in series B funding to advance its pipeline and move into the clinic with a lead program directed against inducible T-cell co-stimulator, or ICOS.

The oversubscribed round, which included investments from Wellington Management Company, Redmile Group, Nextech Invest, Pharmstandard International SA, Cormorant Asset Management, Omega Funds, Casdin Capital, Foresite Capital Management and an undisclosed blue chip public investment fund, was disclosed Thursday, coming on the heels of the American Association of Cancer Research (AACR) meeting in Philadelphia, where immunotherapy presentations reigned supreme. (See *BioWorld Today*, April 17, 2015.)

"It's truly been explosive," acknowledged Richard Murray, CEO of Cambridge, Mass.-based Jounce. "The upshot of this is that it's great for patients, and there have been remarkable and astonishing advances, collectively, from this approach."

Cancer immunotherapy was only beginning to gain ground when Jounce was founded two year ago, the primary achievement at that time being the approval and early commercial success of melanoma drug Yervoy (ipilimumab) from Bristol-Myers Squibb Co. But Third Rock Ventures, the sole investor of Jounce's 2013 \$47 million series A round, believed Yervoy to be the tip of the iceberg. The venture firm spent roughly a year putting together what Third Rock partner Cary Pfeffer called a "dream team of cancer immunotherapy," among them Jounce co-founder and Yervoy researcher James Allison, with the aim of exploring new targets for immunotherapy and finding ways to enhance patient selection. (See *BioWorld Today*, Feb. 14, 2013.)

"Right from the start, the company was really geared at immune-oncology," said Murray, describing Jounce's translational science platform as a "comprehensive understanding of human tumors and the immune system."

Murray took the helm at Jounce last year, bringing to the table his own experience working on Merck & Co. Inc.'s anti-PD-1 drug Keytruda (pembrolizumab), a headliner at the recent AACR meeting.

Immunotherapy, which generally refers to treatment designed to harness the power of the body's own immune system to attack disease, has generated impressive and durable responses in patients. The challenge is that therapies such as CTLA4 inhibitor Yervoy and anti-PD-1 drugs Keytruda and Opdivo (nivolumab, Bristol-Myers Squibb Co.) work in only a minority of patients, and identifying biomarkers has proved tricky business. (See *BioWorld Today*, April 21, 2015.)

That's why Jounce's strategy is twofold: to develop therapeutic programs while also creating methodologies for select patients for treatment, matching them to a drug according to immunotherapy mechanism.

"Since the field is still rather new, still kind of turning the corner

and [has] big expectations, we felt strongly that the emergence of new mechanisms really need to be defined by the patients you're going to treat," Murray told *BioWorld Today*.

"Our line of sight" involves the development of companion diagnostics, though Murray emphasized that Jounce has no intention of becoming a diagnostics company; rather, it will establish the methodologies for selecting patients and then collaborate "with a tried and true partner in the diagnostic space."

Being able to direct patients to specific treatments will mark the next big shift in immunotherapy, "so we see that as a critical principle," he added.

### HEADING TOWARD IND

Proceeds from the series B are expected to see the company's transition toward a clinical-stage firm. "It will allow us to firmly establish our lead program into the clinic, bring a second program into [investigational new drug application]-enabling studies and also expand the discovery work that we will continue to do," Murray said. "So the \$56 million will be pointed in all those directions."

The lead program targeting ICOS stemmed from work by co-founder Allison, who currently serves as chair of the University of Texas MD Anderson Cancer Center Department of Immunology and director of the Immunotherapy Platform.

"The principle is that ICOS functions in the immune system on a certain subset of T cells," Murray explained, specifically appearing on the surface of those T cells after they have been stimulated in a minimal way. Targeting ICOS can signal to those T cells, amplifying that T-cell response to the point it can mediate an antitumor effect. "We can turn up the game and amplify the [immune] system through a monoclonal antibody that selectively activates . . . and amplifies that T-cell response," he said.

Jounce has engineered antibodies targeting ICOS and is in IND-enabling studies, though it hasn't offered a timeline for entering the clinic yet.

And while immediate plans include only testing the ICOS-targeting antibody as a monotherapy, Jounce is well aware of the combo activity happening in the immunotherapy space, including AACR data showing promising responses in patients with metastatic melanoma when combining Opdivo and Yervoy. In addition, a number of companies have inked clinical trial collaborations to test their products in combination with anti-PD-1 drugs – Pfizer Inc.'s Xalkori (crizotinib) and Incyte Corp.'s IDO1 inhibitor INCB24360 are being tested with Merck's Keytruda, while Celldex Therapeutics Inc.'s varlilumab and Five Prime Therapeutics Inc.'s FPA008 are in combo trials with BMS' Opdivo, just to name a few.

Combo therapy "is going to be important," though there is a "somewhat frenzied atmosphere" right now, Murray said. Jounce has tried its ICOS lead candidate in preclinical testing

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differences remain a hurdle. In its 24th year, the Partnerships in Clinical Trials conference started Wednesday, where approximately 1,100 attendees from hundreds of companies are gathering. In recent years, the conference has seen significant growth in the number of attendees from China and South America.

Introducing the track called "Effects of Globalization on Clinical Development," Patricia Flynn Valone, senior director of development operations at the Takeda Development Center in Singapore, recapped themes heard at the PCT Asia conference held in Shanghai last September, emphasizing, "We cannot make the assumption that conducting clinical trials in Asia is the same as conducting clinical trials in the Americas."

China's government, for example, may have different health care priorities than some of the Western governments, such as a focus on diseases more prevalent in the region. Cultural differences, including large patient loads per day, may contribute to difficulties for doctors to find time to conduct clinical trials. Risk-based monitoring is a hot topic, and was scheduled for panel discussion later on Wednesday, Valone said. "It is something to consider certainly in Asia and in China, but please be aware it won't be cheaper. We do need better ways to find potential risk to our data."

### **CHINESE SCIENTISTS RETURNING HOME**

Cory Williams, the head of clinical trial management at Pfizer China R&D Center, commented on the long-recognized trend of Chinese nationals – gaining educations in the West and then working in Europe and the U.S. – who are flocking back to China.

"They have been returning in droves over the last 10 years" to become entrepreneurs through support from the Chinese government and a robust investment community, Williams said. He added that part of the winning strategy is not setting up research and development centers, but by collaborating with academics and emerging biotech companies, giving them commercial prowess. "Indeed, that's where the current evolution is occurring."

Clinical development challenges remain involving revenue, cash flow, patent cliffs, stifled R&D, and the costs to bring new drugs to market – about \$2.8 billion over the first decade of the millennium and about \$4 billion now, Williams said.

But China is transitioning from a country focused on generic therapies to one focused on innovations, and has aspirations this year to have at least 30 innovative new drugs, to be within the top three countries for global patents and medical publications, and to be number one in R&D human resource. It is "well on [its] way to achieving these goals," Williams said.

He also cited significant government investment of ¥40 billion (US\$6.46 billion) and a growing clinical research organization industry, with 24 China-innovated compounds in clinical

development, although the country has a growing but limited number of clinical sites at 400.

Key U.S.-based players in the Chinese region include Beta Pharma Inc., of Princeton, N.J., which started as a contract research organization (CRO) before acquiring assets and starting development of icotinib, an EGFR tyrosine kinase inhibitor targeted for non-small-cell lung cancer. It pursued development in China and the CFDA granted marketing approval under the brand name Conmana. According to the company, it has gained more than a third of the lung cancer therapy market share in China.

"They went from clinic from a first-in-human to market in about five years," Williams said, adding that total development costs were \$30 million to \$50 million, and revenue growth was \$60 million in 2012 and about \$120 million in 2013. "When you look at the return on capital, it's a pretty remarkable story."

Williams finished by explaining that while China's review timelines were once longer than other countries, that is no longer the case, with small molecules gaining approval in as little as six months, and large molecules in a year.

### **INDIA APPROVALS IN 90 DAYS**

Outside of the U.S. and behind China, "India is the second most preferred destination as far as research is concerned," said Arun Maseeh, vice president of medical affairs at India's Cadila Pharmaceuticals Ltd.

Reasons include a large patient pool, as well as its cost efficiency, regulatory conditions and expertise.

As the largest English-speaking country in the southern hemisphere, India's population stands at about 1.2 billion people, making it a prime location for finding clinical trial patients. "There is no such thing as a rare disease in my country," Maseeh said, later adding, "I would have more patients in my country than the rest of the world put together." The country's residents have an average life span of 65 years, and India boasts about 20,000 hospitals, 600,000 doctors and 800,000 nurses.

Maseeh said India's CROs have served companies such as Astrazeneca plc, Eli Lilly and Co., Novartis AG, Pfizer Inc. and others that have offshored operations. The country's regulatory framework offers a speed of randomization of patients that is as "fast or faster than the rest of the world," and in line with China, Maseeh said, adding that India's ethical guidelines for biomedical research provide a high standard and the government is working on initiatives on data exclusivity.

Challenges faced by those working on global clinical trials include dealing with a "multiplicity of authority," Maseeh said, including a lack of harmonization and ambiguities over what is expected. India studies the European Union and U.S. model to address those concerns, he added, and "geared-up" Indian partners provide data acceptable to U.S. and EU regulators.

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## Amgen

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compared to a year ago.

The drugmaker posted a profit of \$1.62 billion, or \$2.11 per share in the quarter, up from \$1.07 billion, or \$1.40 per share a year ago, narrowly beating analyst estimates of \$2.10 per share, according to [Thomson Reuters I/B/E/S](#).

Sales at the Thousand Oaks, Calif.-based company rose about 11.3 percent to \$5.03 billion, compared to \$4.52 billion in year-ago quarter, driven primarily by sales of Enbrel, Prolia (denosumab), Epogen (epoetin alfa), Sensipar (cinacalcet) and Xgeva (denosumab) the company said. Unfavorable changes in foreign exchange rates impacted total revenue and product sales growth by 2 percentage points.

Amgen chairman and CEO Bob Bradway said the earnings growth reflected the company's "discipline in controlling expenses ahead of the launch investments," including next week's planned launch of the recently FDA-approved heart failure drug Corlanor (ivabradine), the launch of Blynicyto (blinatumomab) for patients with relapsed refractory acute lymphoblastic leukemia, and the ongoing rollout of new on-body injector for Neulasta, intended to help the company fend off pending biosimilar competition. (See *BioWorld Today*, April 17, 2015.)

The company said it's also ready to launch the potential blockbuster Repatha (evolocumab) later this year, which could make it the first in its class of protein convertase subtilisin/kexin type 9, or PCSK9, inhibitors to hit the market.

Though Bradway called R&D "a core focus of Amgen" during a conference call following the earnings, the company cut investments in R&D 14 percent to \$856 million from \$994 million in the first quarter of 2014. The saving primarily came as a result of "transformation and process improvements," he said.

The first quarter's strength led executives to raise Amgen's full year guidance for 2015 to between \$9.35 and \$9.65 on sales of \$21.3 billion, compared with its previous estimate of \$9.05 to \$9.40 on revenue of \$20.8 billion to \$21.3 billion.

Despite Enbrel's essential contribution to Amgen's revenue, sales of the therapy fell 17 percent as compared to the fourth quarter of 2014 and competition continues to intensify, particularly in the dermatology space, Amgen said.

Sales of Neupogen also continued to fall, declining 15 percent year over year driven primarily by the impact of competition in the U.S. from Sandoz Inc.'s biosimilar version of the drug Zarxio. (See *BioWorld Today*, March 9, 2015.)

By contrast, global sales of the osteoporosis drugs Prolia and Xgeva grew to a combined \$612 million during the quarter, up 29 percent from a year ago. Prolia sales hit \$272 million in the first quarter, rising 39 percent year over year. More than half of those sales were in the U.S., where Amgen said the drug is now capturing one in three patients starting postmenopausal osteoporosis treatment. Xgeva sales also grew, rising 22

percent year over year to capture \$340 million.

Kyprolis (carfilzomib) made a smaller but growing contribution of \$108 million to the company's sales, up 59 percent year over year. In January, the company submitted a supplemental new drug application to the FDA and a marketing authorization application to the EMA seeking approval to market the proteasome inhibitor for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy.

Even as biosimilar competitions has eroded Neupogen sales, Amgen continues to advance its own programs in the biosimilar space. With positive phase III data for its Humira biosimilar in rheumatoid arthritis behind it, the drugmaker said plans to seek approval later this year for what Sean Harper, Amgen's head of R&D, said would be "the broader label set of indications through the extrapolation mechanism that is consistent with the current guidances." It expects to be in the position to launch the biosimilar in 2017. (See *BioWorld Today*, Feb. 5, 2015.)

### **BRODALUMAB ASTHMA, TREBANANIB STUDIES NIXED**

The company also made the decision to pull the plug on a couple studies. While brodalumab is primarily targeted to psoriasis, where it's expected to capture a significant share of the \$4.3 billion U.S. dermatology biologics space, it fell down in a phase II asthma study, which Amgen said it quit based on futility at a planned interim analysis. The company saw suicidal ideation and behavior in the brodalumab program among patients known to be at risk for those events, said Harper, but didn't see a causal relationship between IL-17 inhibition and suicidal ideation and behavior.

Nonetheless, Harper said the topic "will be an important and appropriate focus of regulators in their analysis of the risk/benefit profile during their review of the applications we plan to file for brodalumab."

In another study, a phase III trial of trebananib in first-line ovarian cancer, Amgen decided to stop dosing patients with the drug based on the recommendation of the trial's data safety monitoring committee, which deemed the study unlikely to achieve its primary progression-free survival endpoint.

Despite the setbacks, analysts read the company's overall earnings report as a net positive. With multiple launches expected over the next two years, said Deutsche Bank analyst Robyn Karnauskas, Amgen has the potential to generate peak revenues of greater than \$10 billion.

Amgen's shares (NASDAQ:AMGN) rose 64 cents, closing at \$169.10 on Wednesday. //

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The partnerships provide a gateway for communication with regulators.

That gateway can speed the timeline to approval by Indian regulators. When working with a local partner, the time from submitting a dossier for approval and getting to the next step, which is sometimes approval itself, "is approximately 90 days," Maseeh said.

The event, which continues through Friday, is hosted by the Institute for International Research USA in an effort to join clinical research with open innovation. //

## Jounce

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with an anti-PD-1 drug with promising pharmacology results. "So that's clearly in the plans," he said, "but there may be other ways to do this that start to cross some of the disciplines." Instead of two monoclonal antibodies, for instance, the most efficacious combo might be a monoclonal antibody plus a vaccine.

Jounce also has its eye on immunotherapies that go beyond T cells.

"Most of the success we've witnessed" – Yervoy, Keytruda, Opdivo – "is really pointed at the T-cell aspect of the immune system," Murray noted. "And we are certainly believers in that. But beyond that we're starting to focus a discovery program into tumor immune suppressant mechanisms that are not directly related to T-cell but to other components of the immune system.

"It's an important step for the field," he added. "If that comes to fruition, we'll have the opportunity to reach a . . . greater number of patients with effective immunotherapy."

The firm, which currently has about 37 employees, is expected to grow. "We have a really terrific group of researchers and translational teams," Murray said. "Now, we're really starting to hire in more people at the development stage."

Given its success in attracting venture funding and the robust capital markets, Jounce is looking to retain product rights, at least until the human proof-of-concept data, an "enormous inflection point," he said. Then "whether we partner really will have to be the devil in the details. But on reaching the point of inflection of human proof of concept, the company has a number of options," such as partnering or going an IPO route.

"That first year, [the company] was creating an atlas of the human immune system and tumors," Murray added. "That speaks to the long-term nature of the company and a desire to be in business."

He called that approach characteristic of Third Rock-funded companies, providing "a large series A that allows companies to establish a footprint to do just that." //

## Potenza

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A humanized monoclonal antibody invented at MD Anderson, h8F4, is the focus of the pact. The antibody targets an HLA-restricted peptide called PR1/HLA-A2, which is expressed in cancer cells and cancer stem cells.

Late last year, Astellas made public a three-year collaboration with the Dana-Farber Cancer Institute to research and develop small-molecule inhibitors of oncogenic K-ras for the treatment of cancer, including lung cancer. K-ras is the most commonly mutated oncogene in human cancers, with about 30 percent of all cancers harboring activating ras mutations, which make them particularly hard to treat.

Cancer immunotherapy, where Potenza puts its efforts, "is a field that's been around for a long time, but until recently the understanding of these immune checkpoints and how to overcome them to help the immune system attack tumors" was unrefined, Hicklin noted. "Just a few years ago, there was very little clinical benefit, for example, in melanoma," and now the promise has extended to tumors of the lung and others. "It's also clear that there are multiple ways to activate the immune system to target some of these immune suppressive mechanisms," he said. "That's why you see all these companies getting into the field." In March 2011, the FDA approved Yervoy (ipilimumab, Bristol-Myers Squibb Co.) for metastatic melanoma. (See *BioWorld Insight*, April 4, 2011.) //

## FINANCINGS

Oberland Capital, of New York, an investment firm focused on the global health care industry, said it closed Oberland Capital Healthcare, an inaugural royalty and credit opportunities fund, with \$425 million in capital commitments. Concentrating on the biopharmaceutical, medical device and diagnostic sectors, Oberland Capital provides customized financing solutions and targets investments ranging from \$15 million to \$100 million with the ability to execute substantially larger transactions.

## OTHER NEWS TO NOTE

**Biotime Inc.**, of Alameda, Calif., said it inked a nonexclusive license agreement between its subsidiary, ES Cell International Pte Ltd., and Beckman Research Institute of the City of Hope (BRICOH) through which ESI's clinical-grade human embryonic stem (hES) cells will be manufactured and provided to BRICOH's clinical collaborators, including medical research organizations intent on using the hES cells to develop and commercialize therapeutic products to treat human disease. Specific financial terms were not disclosed, but the licenses may entitle Biotime to receive additional revenues such as milestone payments related to the attainment of clinical trial and commercial milestones and royalties on product sales. Biotime and its subsidiaries will retain the rights to manufacture their own stem cell-based products as well as to license rights to other third parties.

## AAN

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prospects cited by Cudkowicz. The Pasadena, Calif.-based company approached the agency to request accelerated approval for GM604 on the basis of a randomized, double-blind, placebo-controlled phase IIa trial that enrolled 12 patients with ALS.

The company presented data in April 2014 showing that 10 weeks following completion of dosing without further treatment, clinical measurements of ALS disease progression remained unchanged from baseline in two of eight treated patients, but the rates of degradation in clinical measures slowed in the other six. Genervon subsequently reported additional details, including publication of findings in January that showed improvements from baseline to week 12 in clinical observations after a six-dose treatment of GM-604, including clearer articulation in a patient's speech video and swallow volume compared to baseline.

Although the findings appeared largely observational, Genervon issued a press release last month outlining its regulatory approach and reiterating the findings, which it called statistically significant. The company emphasized the urgency of gaining accelerated approval, noting in its release, "even though the FDA has promised to help Genervon expedite the approval process for a phase III trial, it would still take at least three years for GM604 to reach [new drug application]. This means the majority of this generation of ALS patients would not survive to try GM604."

Last Friday the FDA released a public statement on ALS that called on Genervon "to release all the data from their recently completed trial in order to allow a more informed discussion of the trial findings among ALS stakeholders. Such a release should include the pre-specified clinical outcome measures as assessed by change from baseline observations that were taken just prior to randomization to drug or placebo."

Genervon officials did not attend the AAN and declined additional comment on the matter beyond citing their press releases and a link to the scientific rationale and trial data on the company's website.

#### **'WE HAVE TO STAND UP FOR PATIENTS'**

Cudkowicz also steered clear of the controversy in her presentation. But prominent ALS researcher Stanley Appel, chairman of neurology at Houston Methodist Hospital and director of the Houston Methodist Neurological Institute and the hospital's MDA/ALS Clinic, echoed many in the ALS community by siding with the FDA.

"Everyone's hanging by their thumbs with this issue," Appel told *BioWorld Today*. "The company is pushing this on Capitol Hill and everywhere else, and there are no data. The FDA has made a logical request: 'Show us the data.'"

A 12-week study with findings in eight patients isn't sufficient to draw conclusions about the efficacy or even the safety of an ALS

drug, Appel maintained.

"I fully understand the sense of urgency," he said. "I deal with this every week with our patients. They want access to everything."

But drug companies targeting ALS must meet the same standards as those pursuing therapies in larger indications, despite the challenges outlined by Cudkowicz, Appel maintained, charging that failure to do so could cause physical, financial and/or emotional harm to patients and their families.

"We've been through this so often in ALS," Appel said, citing the laundry list of failures in the space, including some drug candidates that caused more harm to patients than placebo. "At some point, we have to stand up for patients and protect their interests."

In some ways, efforts to treat ALS effectively mirror the rapid evolution of personalized medicine, in which "it is quite clear that dramatic advances have been made in determining mutant genes, and we are learning how we can deal with these individual genes" by down-regulating them, Appel said. "This is very, very exciting."

But the challenge for the scientific community is that multiple genes implicated in ALS can produce the same clinical phenomena, while a single gene can produce multiple clinical manifestations.

"We're getting more evidence that the process is not cell autonomous, but non-cell autonomous," he said, with mutated genes altering the rate at which motor neurons are damaged but not necessarily the mechanics of that process.

For drug development in ALS, that may mean a sharper focus on targeting what's already known about degeneration of the motor neurons, such as down-regulating mutant superoxide dismutase, or SOD, according to Appel. Therapies to target this gene using antisense oligonucleotides or viral vectors with RNAi are on the front burner. (See *BioWorld Insight*, Oct. 20, 2014.)

Efforts to "reprogram" the immune system and tamp down ALS also need more attention, according to Appel, who acknowledged his bias for pursuing this approach rather than seeking to find additional genes of interest.

"I'm all in favor of further genetic exploration," he said. "But it's now been more than 20 years since we knew that mutant SOD causes ALS, and there is not a single therapy for patients. If we couldn't develop a therapy targeting a common gene like SOD, how are we going to target all of these other genes?"

In other AAN news:

**Acorda Therapeutics Inc.**, of Ardsley, N.Y., presented data from a phase I trial of rHlgM22, its remyelinating antibody in development to treat multiple sclerosis (MS), showing the candidate was well tolerated in each of five tested doses and no serious adverse events occurred at any dose level. In its poster presentation, the company also reported that rHlgM22 was detected in cerebrospinal fluid, indicating the drug's access to

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## AAN

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the central nervous system. The placebo-controlled, single-dose, escalating study in 72 patients with clinically stable MS was designed to explore dose tolerability for six months following treatment. Acorda plans to advance the drug next into a study in MS patients experiencing acute relapses. On Wednesday, the company's shares (NASDAQ:ACOR) fell \$1.33 to close at \$33.34. (See *BioWorld Today*, April 21, 2015.)

**Isis Pharmaceuticals Inc.**, of Carlsbad, Calif., reported data from an ongoing open-label extension (OLE) study of ISIS-TTRx in patients with familial amyloid polyneuropathy (FAP) who completed the company's ongoing phase III study. An analysis conducted on the first group of patients to reach three months of treatment in the OLE study showed a reduction in transthyretin (TTR) protein levels up to 92 percent with a median reduction of 78 percent compared to patients' baseline TTR levels at entry into the phase III study. In the platform presentation, the lead investigator reported that reductions of up to 92 percent in TTR protein were reported in the first 13 patients to enter the OLE study, following 13 weeks of treatment with ISIS-TTRx. The antisense drug also was featured in a second platform presentation in which the company provided an overview of the program, including findings from the phase I trial.

**Phasebio Pharmaceuticals Inc.**, of Malvern, Pa., reported preclinical data in a poster presentation showing that PB1046 ameliorated Duchenne muscular dystrophy (DMD) myopathies, slowed cardiac deterioration and protected skeletal muscle by reducing fibrosis in DMD models. PB1046 is designed to work as a stable and long-acting vasoactive intestinal peptide receptor agonist. (See *BioWorld Today*, March 13, 2015.)

**Ultragenyx Pharmaceutical Inc.**, of Novato, Calif., presented data from an investigator-sponsored trial of triheptanoin (UX007) to treat movement disorders associated with glucose transporter type-1 deficiency syndrome (Glut1 DS), also known as De Vivo disease. The open-label trial enrolled eight Glut1 DS patients between 7 and 47 years old with non-epileptic paroxysmal manifestations. Patients completed comprehensive diaries to record motor and non-motor events and a clinical global impression scale during a baseline, treatment and withdrawal phase, each lasting two months. In the poster presentation, investigators reported that, during the baseline phase, patients experienced, on average, 31 paroxysmal manifestations, including 16 dystonic events. During the triheptanoin treatment phase, patients reported a statistically significant 90 percent reduction in these events, to an average of three paroxysmal manifestations, including two dystonic events ( $p = 0.028$ ). In the withdrawal phase, when triheptanoin treatment was discontinued, the rate of paroxysmal manifestations increased substantially, to an average of 24 events per patient, including 12 dystonic events ( $p = 0.043$ ). Triheptanoin was well tolerated in all patients. Six patients

completed the study. Ultragenyx said it plans to initiate a confirmatory randomized, double-blind, placebo-controlled study of triheptanoin in the Glut1 DS movement disorder phenotype. The company expects to meet with the FDA on final study design details in the second half of 2015. On Wednesday, the company's shares (NASDAQ:RARE) gained \$2.74 to close at \$66.96. //

### OTHER NEWS TO NOTE

**Capricor Therapeutics Inc.**, of Los Angeles, said it was granted FDA orphan designation for its cell therapeutic candidate, CAP-1002, for the treatment of cardiomyopathy associated with Duchenne muscular dystrophy (DMD). CAP-1002, comprising cardiosphere-derived cells, is in development as a potential therapeutic approach for the treatment of DMD-associated cardiomyopathy. The cells have been shown to promote cardiomyogenesis and angiogenesis, while inhibiting oxidative stress, inflammation and fibrosis in preclinical studies. The company said it expects to file an investigational new drug application for CAP-1002 in the near future.

**Cellular Biomedicine Group Inc.**, of Shanghai, said it signed a new five-year lease for a 15,000 sq. ft. site slated for their third GMP facility in anticipation of growth in the Beijing vicinity and further development of their CAR-T platform. Approximately half of the site will be a GMP equipped facility to support clinical batch production and commercial scale manufacturing.

**Clearside Biomedical Inc.**, of Alpharetta, Ga., said it acquired Menlo Park, Calif.-based **Iscience Interventional Corp.**'s patent portfolio covering drug delivery to the suprachoroidal space (SCS). That is expected to complement Clearside's own intellectual property portfolio which protects its drug candidates, microinjector and non-surgical drug administration into the SCS. Terms were not disclosed. Clearside develops drug therapies to treat chronic, blinding diseases of the eye, with product candidates focusing on diseases affecting the retina and the choroid.

**Corbus Pharmaceuticals Holdings Inc.**, of Norwood, Mass., said it received a development award for up to \$5 million from Cystic Fibrosis Foundation Therapeutics Inc., the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation, to support a phase II trial of the company's oral anti-inflammatory drug, Resunab, in adults with cystic fibrosis. The trial is set to start this quarter, pending FDA approval of the protocol. Resunab is a synthetic drug designed to bind to the CB2 receptor and has been shown to resolve inflammation and progressive fibrosis in preclinical models.

**Cymabay Therapeutics Inc.**, of Newark, Calif., said the FDA granted orphan drug designation for MBX-8025, a selective peroxisome proliferator-activated receptor delta agonist, to treat patients with hyperlipoproteinemia types I or V (Fredrickson classification). The FDA recently also granted orphan designation for MBX-8025 to treat patients with homozygous familial hypercholesterolemia, and a phase II study in that indication is slated to start this quarter.

**OTHER NEWS TO NOTE**

**Ligand Pharmaceuticals Inc.**, of San Diego, said it earned a \$500,000 milestone payment from **Sage Therapeutics Inc.**, of Cambridge, Mass., linked to the treatment of the first patient in Sage's phase III open-label expanded access protocol study. Designated study 302 is designed to offer SAGE-547 to patients affected by super-refractory status epilepticus (SRSE) and to evaluate the safety of the compound in patients with SRSE. Ligand entered into a Captisol license agreement with Sage for the development and commercialization of SAGE-547 in 2011.

**Novogen Ltd.**, of Sydney, said Cantx Inc., its joint venture company with Yale University, received FDA orphan drug status for chemotherapy candidate Cantrixil in ovarian cancer. The company reported preclinical data at the American Association of Cancer Research meeting in Philadelphia, showing that, in an animal model believed to be highly representative of late-stage chemo-resistant ovarian cancer, Cantrixil resulted in a greater than 95 percent tumor reduction. Cantrixil is a cyclodextrin envelope containing the active ingredient TRXE-002 and is designed as an intra-cavity chemotherapy to be injected directly into the peritoneal and pleural cavities without causing local irritation or toxicity.

**Paxvax Inc.**, of Redwood City, Calif., said it inked a series of new commercial partnerships and distribution agreements for its commercial typhoid vaccine Vivotif. Since its acquisition of Vivotif in July 2014, Paxvax has established legal entities and commercial infrastructure in Italy, Spain and Switzerland and the UK and, in countries where the firm does not maintain its own commercial operations, has signed agreements for the sale, marketing and distribution of Vivotif. No financial terms were disclosed.

**Regen BioPharma Inc.**, of San Diego, said it has engaged Charles River Laboratories to initiate a good laboratory practices (GLP) mouse toxicity study on Hemaxellerate, a cellular drug under development and designed to heal damaged bone marrow. The company has developed a protocol for assessing safety of the product in mice lacking an immune system.

**Solaranrx Inc.**, of Albuquerque, N.M., said the FDA granted orphan status to lead candidate SRX-1177 for the treatment of stage IIB to IV malignant melanoma. Solaranrx's technology is designed to precisely target melanoma tumors with a radiolabeled peptide that selectively attaches to melanocortin-1 receptors overexpressed on about 80 percent of melanoma samples. SRX-1177 is in preclinical development.

**Tekmira Pharmaceuticals Corp.**, of Vancouver, British Columbia, said preclinical data highlighting positive results against Ebola virus Makona infection using a newly adjusted siRNA cocktail have been published in *Nature*. The company, along with its collaborators at the University of Texas Medical Branch at Galveston, jointly conducted a preclinical study

demonstrating 100 percent survival of nonhuman primates infected with the West Africa Makona strain of Ebola virus, previously referred to as the Guinea strain. Complete survival was observed even when treatment did not begin until three days after viral exposure, a time point at which animals were five to six days away from death. TKM-Ebola-Guinea (targeting the Makona strain), containing the adjusted siRNA cocktail used in the preclinical study, is currently being evaluated in a phase II study in Sierra Leone with results expected in the second half of this year.

**Vical Inc.**, of San Diego, said it entered a \$4 million contract with the Swiss nonprofit foundation IPPOX Foundation to manufacture HIV-antigen plasmid DNA as a component of vaccine regimens to be evaluated in clinical trials for the prevention of HIV infection. IPPOX helps conduct HIV vaccine clinical trials under the auspices of the Pox-Protein Public-Private Partnership, funded by the Bill & Melinda Gates Foundation and the National Institute of Allergy and Infectious Diseases. The new contract, which builds upon Vical's 2010 agreement with IPPOX to manufacture plasmid DNA for HIV vaccine clinical trial, is expected to use those plasmids as priming components of prime/boost vaccine regimens for evaluation in phase I studies and potentially in a phase IIb trial. Vical expects material delivery to begin in the fourth quarter of 2015.

**IN THE CLINIC**

**Genocea Biosciences Inc.**, of Cambridge, Mass., completed enrollment in its phase IIa human-challenge study of GEN-004, Genocea's universal vaccine candidate for the prevention of infection by all serotypes of pneumococcus. The company anticipates reporting top-line data from this study in 98 subjects in the fourth quarter of 2015.

**Globeimmune Inc.**, of Louisville, Colo., said a randomized phase II trial designed to investigate the safety and efficacy of GI-6301 in combination with radiation therapy in patients with chordoma is open for enrollment at the National Cancer Institute. The company said the GI-6301 Tarmogen, exclusively licensed to **Celgene Corp.**, of Summit, N.J., has demonstrated promising initial results in chordoma patients evaluated in a recent phase I study.

**Norgine BV**, of Amsterdam, the Netherlands, presented the study design of PROSPER, an outcomes study of hepatic encephalopathy patients' experiences on rifaximin- $\alpha$  550mg at the International Liver Congress 2015. PROSPER is an observational, multicenter study of 550 patients in Europe and Australia. It has been designed to monitor the clinical effectiveness of rifaximin- $\alpha$  and its impact on health care resources utilizations. The company said it expects that the findings of this study will provide real-world evidence, a better understanding of the burden and natural history of hepatic encephalopathy and the variability in disease management in individual units.

**IN THE CLINIC**

**Nuvo Research Inc.**, of Mississauga, Ontario, disclosed details of its new phase II trial (the 2015 WF10 Trial) to assess WF10 for the treatment of allergic rhinitis. The trial will be a randomized, double-blind, placebo-controlled, single-center study to assess the efficacy, safety and tolerability of a regimen of five WF10 infusions. The trial will enroll patients who have a moderate to severe allergy to grass and ragweed pollen. It's expected to enroll approximately 146 patients and to be completed with top-line results available in late in the fourth quarter of this year or early next. WF10 is a solution containing stabilized chlorite ions that focuses on supporting the immune system by targeting the macrophage, a type of white blood cell that coordinates much of the immune system, to regulate normal immune function, the company said.

**Oncomed Pharmaceuticals Inc.**, of Redwood City, Calif., began dosing patients in its randomized phase II trial of demcizumab (OMP-21M18) in patients with first-line metastatic pancreatic cancer. The trial, called YOSEMITE, will compare the efficacy and safety of demcizumab combined with standard of care Abraxane (nab-paclitaxel, Celgene Corp.) plus gemcitabine in patients with first-line metastatic pancreatic cancer. The primary endpoint is progression-free survival. Secondary endpoints include overall survival, response rate, duration of response, safety, immunogenicity and pharmacokinetics. Oncomed is eligible for a \$70 million milestone from Celgene Corp. for successful completion of an interim safety analysis in YOSEMITE and another trial in non-small-cell lung cancer trial, called DENALI. That analysis is expected to occur in late 2015 or early 2016, the company said. (See *BioWorld Today*, Sept. 2, 2014.)

**Orexo AB**, of Uppsala, Sweden, reported that Zubsolv (buprenorphine/naloxone), its sublingual tablet for the maintenance treatment of opioid dependence, appeared safe and effective at the conclusion of a 24-week open-label follow-up study that included 665 subjects. At baseline of parent studies, Orexo's Study 006 and Study 007, conducted before treatment was initiated, the enrolled opioid-addicted patients' mean opioid craving score was 70.8 and, by week 24, the mean score had been improved to 10.9 in patients who completed the study.

**Pharmaleads SAS**, of Paris, said the first patient has been included in a phase IIa study of oral PL37 in diabetic neuropathy. PL37, a dual enkephalinase inhibitor (DENKI), specifically targets the nociceptors located on peripheral nerve endings. They increase the concentrations of enkephalins (endogenous morphine) only where they are produced in large concentrations in response to a painful stimulus. In the absence of PL37, enkephalins are very rapidly inactivated by enkephalinases. By inhibiting these enzymes, DENKIs induce lasting analgesic effects, as potent as those of morphine but without its side effects. The clinical study will recruit 108 patients with diabetic neuropathy and poor pain relief provided by pregabalin or gabapentin, the most commonly prescribed treatments for neuropathic pain. This study aims

to demonstrate the superiority of PL37 vs. placebo, when administered in combination with the standard treatment for diabetic neuropathy.

**Regeneus Ltd.**, of Sydney, received ethics approval for a phase I trial of its new off-the-shelf allogeneic stem cell treatment, Progenza, for patients with osteoarthritis of the knee. The randomized, double-blind, placebo-controlled single-ascending-dose study will include 20 participants. The primary endpoint is an evaluation of safety and tolerability. The secondary objectives are to investigate the effect of Progenza on knee pain and function; quality of life; knee joint structures using magnetic resonance imaging; and osteoarthritis biomarkers. Participants will be monitored for 12 months with an interim safety review at one month after treatment.

**Strategia Therapeutics Inc.**, of Boston, said it started a phase I/IIa trial of anticancer agent E6201 in patients with advanced hematologic malignancies, including relapsed or refractory acute myeloid leukemia (AML), high-risk myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). E6201, discovered by **Eisai Co. Ltd.**, of Tokyo, and licensed by Strategia, is a dual-inhibitor of FMS-like tyrosine kinase 3 (FLT-3) and mitogen-activated protein (enzyme) kinase (MEK). Activation of FLT3 is observed in patients with AML carrying either internal tandem duplication (ITD) or point (D835) mutations in the FLT3 gene, and E6201 has demonstrated activity against both mutations. The Ras/Raf signaling pathway signals through the downstream signal transducers MEK1 and extracellular signal-related kinases (ERK) and activation of this pathway is seen in AML cells of patients failing FLT3 inhibitor therapy.

**Triphase Accelerator Corp.**, of San Diego and Toronto, started a phase I proof-of-concept study of its Summit, N.J.-based **Celgene Corp.**-partnered proteasome inhibitor marizomib. The study is evaluating an I.V. formulation of the potential therapy in combination with Avastin (bevacizumab, Genentech Inc./Roche AG) in patients with glioblastoma, the most common and aggressive malignant primary brain tumor. Subjects in the study are in their first or second relapse and have not previously received any Avastin or other anti-angiogenic agent or proteasome inhibitor. If successful, the open-label, multicenter, dose-escalation trial will support the design of a larger-scale proof-of-concept study. (See *BioWorld Today*, Nov. 12, 2014.)

**PHARMA: OTHER NEWS TO NOTE**

**Bayer HealthCare Pharmaceuticals Inc.**, of Whippany, N.J., said the FDA has accepted the filing of a supplemental biologics license application for Betaconnect (proposed name), another delivery option for Betaseron (interferon beta-1b), a treatment for relapsing-remitting multiple sclerosis.

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**AACR 2015**

The following data were released at the American Association for Cancer Research Annual Meeting in Philadelphia:

**Acetylon Pharmaceuticals Inc.**, of Boston, reported that preclinical data evaluating combinations of its selective histone deacetylase (HDAC) 6 inhibitors, ricolinostat and ACY-241, with Pomalyst (pomalidomide, Celgene Corp.) and Revlimid (lenalidomide, Celgene Corp.), showed that they work together to increase cell death in multiple myeloma and mantle cell lymphoma. The company said that the mechanism of action suggested by the studies appears to be reduction of the oncogenic transcription factors, MYC and IRF4, both known to be major drivers of B-cell malignancies, as well as other cancers. Acetylon also said it is starting a phase Ia/Ib multicenter, single-arm, open-label, dose escalation study of ACY-241. The trial is designed to determine the maximum tolerated dose and evaluate the safety and preliminary antitumor activity of ACY-241 as monotherapy and in combination with pomalidomide and low-dose dexamethasone in eligible patients with relapsed or relapsed and refractory multiple myeloma.

**Bind Therapeutics Inc.**, of Cambridge, Mass., released data on the company's lead Accurin drug candidate, BIND-014, and the Accurin drug candidate AZD2811, which is being developed in collaboration with **Astrazeneca plc**, of London. The data demonstrate the ability of Accurins to control biodistribution and accumulate in target tissue across a broad spectrum of therapeutic payloads, the company said. In a poster presentation titled, Bind researchers presented clinical and preclinical data demonstrating that the Accurin BIND-014 provided prolonged circulation and controlled release of encapsulated docetaxel when compared to conventional docetaxel consistently across multiple species. The controlled biodistribution and potential for targeted and preferential tumor accumulation may result in increased efficacy and decreased toxicity with BIND-014. In another poster, data demonstrated that the Accurin nanoparticle AZD2811 exhibits promising in vivo and in vitro tumor growth inhibition as monotherapy in diffuse large B-cell lymphomas and small-cell lung cancer. The data also indicate that AZD2811 has the flexibility to be delivered with different doses/schedules, offering the potential to adapt the therapeutic regimen to different tumors while achieving an improved therapeutic index.

**Biothera Inc.**, of Egan, Minn., presented data showing its investigational cancer immunotherapy Imprime PGG enhances the function and proliferation of T cells that play a critical role in the fight against cancer. Specifically, Biothera researchers demonstrated that plasma from Imprime PGG-treated whole blood was able to reduce the ability of regulatory T cells to suppress CD4+ T cells, and enhanced the proliferation of both CD4+ and CD8+ T cells in response to in vitro stimulation. This T cell expansion was accompanied by up-regulation of the transcription factor T-bet and increased production of the

potent anti-tumor cytokine interferon gamma, suggesting Imprime PGG may drive polarization of T cells to a Th1, anti-tumor phenotype, the company said. Proof of concept with the therapy has been established in phase II trials.

**Celator Pharmaceuticals Inc.**, of Ewing, N.J., presented data on combining CPX-351 with approved anti-leukemia drugs such as fludarabine as well as other molecularly targeted agents such as the Chk1 inhibitors MK-8776 and LY2603618 to treat acute myeloid leukemia (AML) and other blood cancers. In both cases, the combined agents complemented each other's anti-leukemic properties, resulting in an enhanced overall effect. When fludarabine and CPX-351 were exposed to leukemia cells, intracellular concentrations of cytarabine triphosphate (Ara-CTP) were increased by two- to threefold. Chk1 inhibitors and CPX-351 synergized to induce increased DNA fragmentation and apoptosis, leading to increased (as high as 10-fold) leukemia cell kill in a number of AML lines as well as in AML patient blasts. Together, the results provide evidence that CPX-351 may combine favorably with a wide range of agents to achieve enhanced anti-leukemic effects.

**Curis Inc.**, of Lexington, Mass., presented data from in vitro and in vivo studies for CUDC-427, an antagonist of inhibitor of apoptosis (IAP) proteins. CUDC-427 is being studied in a phase I trial in patients with advanced solid tumors or lymphoma. The first poster, "Predictive biomarker signatures for IAP inhibitor CUDC-427," discussed data from in vitro and in vivo studies that were conducted to identify predictive gene signatures that may be associated with drug response in ovarian and breast cancers. The drug response and genomic/expression profiles of 29 breast and ovarian patient-derived xenografts (PDX) were used to generate a set of gene signatures that will be further validated in additional PDX models and patient samples derived from ongoing clinical testing of CUDC-427. The second poster, "IAP inhibitor CUDC-427 induces tumor regression or stasis in preclinical models of B-cell lymphoma," reported data from in vitro and in vivo studies showing CUDC-427 anti-tumor activity in multiple hematologic cancer models, including diffuse large B-cell lymphoma (DLBCL). Data from a panel of human hematologic cell lines showed that the DLBCL cell lines were most sensitive to CUDC-427 treatment in growth inhibition assays. The anti-tumor effect of CUDC-427 was further confirmed in in vivo studies where daily dosing of CUDC-427 induced tumor regression or stasis in certain DLBCL xenograft and B-cell lymphoma syngeneic mouse models. Curis' collaborator, Aurigene Discovery Technologies Ltd., also reported preclinical data on its interleukin-1 receptor association kinase-4 (IRAK-4) inhibitor program that included data from multiple chemically distinct series of potent oral IRAK-4 inhibitors. These compounds were shown to potently inhibit IRAK-4 kinase activity in biochemical assays as well as proliferation of MYD88 mutant DLBCL cell lines.

**Deciphera Pharmaceuticals LLC**, of Waltham, Mass., presented data on its most advanced drug candidates including

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altiratinib, an inhibitor of MET/TRK/TIE2 and VEGFR2 kinases and rebastinib, a TIE2 inhibitor, and on the company's work with **Eli Lilly and Co.**, of Indianapolis, on pan-RAF inhibitors. In a poster presentation entitled "Altiratinib is a potent inhibitor of TRK kinases and is efficacious in TRK-fusion driven cancer models," researchers demonstrated that altiratinib potently inhibited TPM3-TRKA and ETV6-TRKC fusion protein activation and cell proliferation in tumor cell lines. TRK kinases are implicated in a variety of cancers in which TRK gene fusions have been shown to drive tumor growth. Altiratinib is currently in a phase I clinical trial in patients with solid tumors. In a poster presentation titled, "Rebastinib potently inhibits function of perivascular TIE2 expressing macrophages in vitro and in vivo," researchers reported that rebastinib, a selective TIE2 kinase inhibitor with picomolar potency, completely blocked TIE-2 expressing macrophage (TEM)-induced tumor cell invasion. TEMs are a population of highly protumoral macrophages that facilitate tumor growth, angiogenesis, invasion, and immunosuppression. Rebastinib has completed a first-in-human study and will enter a phase Ib study in the second half of 2015. In a poster titled, "Mouse PDX trial suggests combination efficacy of Raf and EGFR inhibition for colorectal cancer with BRAf or KRas mutation," preclinical results were presented on LSN3074753, a pan-RAF inhibitor developed by Deciphera in collaboration with Lilly. This program is currently in phase I clinical development. Synergy was found in a subset of colorectal cancers by combining the pan-RAF inhibitor, which has been shown to inhibit mutant KRAS and BRAF tumor cell drivers that occur in approximately 70 percent of colorectal cancer patients, with the anti-EGFR antibody cetuximab. When evaluated in a collection of 78 patient-derived xenograft models of colorectal tumors, the overall disease control rate in the combination arm was 50 percent (39/78), while cetuximab or LSN3074753 alone had an overall DCR of 24 or 18 percent, respectively.

**Navidea Biopharmaceuticals Inc.**, of Dublin, Ohio, reported data showing that the Manocept molecule selectively binds to, and is continuously internalized by, tumor-associated macrophages and Kaposi's sarcoma (KS) tumor cells in a preclinical model. Preliminary results from a clinical study also demonstrated that a single, subcutaneous injection of Technetium Tc 99m tilmanocept (Navidea's Lymphoseek), an FDA-approved Manocept-based imaging agent, detects and localizes in KS tumors and the lymph nodes involved in draining the KS tumor fields.

**Threshold Pharmaceuticals Inc.**, of South San Francisco, presented preclinical data on TH-4000, its molecularly targeted, hypoxia-activated, irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that suggest it may overcome resistance to therapy with conventional EGFR-TKIs. In a xenograft model of non-small-cell lung cancer (NSCLC) in which both wild-type EGFR and mutant EGFR are present, TH-4000 was more active than the

conventional EGFR-TKI erlotinib. Complete tumor control was observed in this model using human-equivalent doses of TH-4000 that were less than 15 percent of the maximum-tolerated dose defined previously in a phase I trial. The company contended the data support its planned phase II trials, including one in patients with EGFR-positive, T790M-negative NSCLC and the other in patients with recurrent/metastatic head and neck cancer.

**Verastem Inc.**, of Boston, presented data, which provide continued evidence that VS-6063, VS-4718 and VS-5584 effectively target cancer stem cells, reduce tumor initiating capability and prolong the anti-tumor response to standard of care chemotherapy in preclinical models of multiple tumor types. The results from these studies support both ongoing and planned clinical trials. In one of those presentations, FAK inhibitors VS-6063 and VS-4718 target cancer stem cells: Implications for TNBC sequential and combination therapies, Verastem's VS-6063 and VS-4718, diminished cancer stem cells (CSC) in vitro, ex vivo and in xenograft models in contrast to paclitaxel or cisplatin treatment which enriched CSCs. Consistent with the notion that CSCs are responsible for cancer relapse after chemotherapy, VS-6063 and VS-4718 substantially delayed tumor growth following cessation of paclitaxel or cisplatin treatment in models of triple negative breast cancer. Additionally, both VS-6063 and VS-4718 inhibited metastatic outgrowth and/or induced regression of metastases after primary tumor resection.

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