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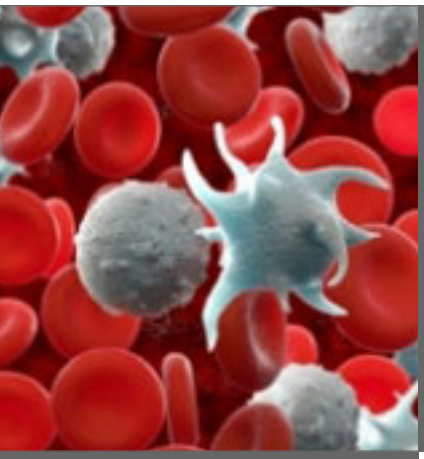

BIO International Convention 2017

Fit to be tried: Rationale's lacking in I-O attempts but personalized ploy may win

By Randy Osborne, Staff Writer

SAN DIEGO – Although "it's going to be a bit of a bumpy road" and the process "won't be as pretty as we would like it to be," clinicians have reached "a point where I think we can start to mix and match the appropriate mechanisms" of immuno-oncology drugs to fit individual patient needs, said Tim Reilly, head of early asset development in oncology for Bristol-Myers Squibb Co. (BMS), of New York.

See Personalized med, page 3

Advocates tell their stories, struggles, to inspire a patient-centric culture

By Karen Pihl-Carey, Analyst

SAN DIEGO – As scientists and business leaders discussed innovation, valuation, transformative therapies and coming epidemics in various rooms throughout the San Diego Convention Center, something different occurred in Room 5B on Wednesday afternoon during BIO's International Convention.

Four people gathered on stage to give a voice to the patient.

See Advocacy, page 4

NIH grants critical to de-risk programs, attract more capital

By Tamra Sami, Staff Writer

SAN DIEGO – Recent policy changes are more favorable for small companies looking for startup funds, and the NIH is a good place to start.

NIH grants for small life sciences companies doubled in 2016, and Congress has reauthorized the Small

See NIH, page 5

Novartis shoots a hoop with Ilaris in cardiovascular outcomes study

By Cormac Sheridan, Staff Writer

DUBLIN – Novartis AG looks to be on course to add another significant product to its portfolio of cardiovascular drugs following a positive readout from the Cantos phase III cardiovascular outcomes trial of its interleukin-beta1 (IL-beta1)

See Novartis, page 6

Repare raises $68M to join CRISPR-based hunt for synthetically lethal mutations

By Cormac Sheridan, Staff Writer

DUBLIN – After 18 months in stealth mode, Montreal-based Repare Therapeutics Inc. has emerged with $68 million in series A funding and serious ambitions to become a leader in identifying small-molecule drugs that act on

See Repare, page 8

BIO International Convention 2017

Aligned interests bond ex-U.S. investors and U.S. biotechs, but not without friction

By Michael Fitzhugh, Staff Writer

SAN DIEGO – Ambitious venture funds from Russia, China and India are seeking a growing stake in U.S. companies, creating new access to capital for startups. Though offering value beyond money to both investors and the recipients of their funds, international venture capitalists speaking at BIO 2017 said cultural and political frictions can still create challenges.

Look no further than Allergan plc's 2016 buyout of Ann Arbor, Mich.-based Retrosense Therapeutics LLC for nearly $600 million to see why investors like Moscow-based RBV Capital find U.S. investing so attractive. "The pre-money was much, much lower," said panelist Alexey Konov, CEO of RBV and a partner at the firm. "We think the U.S. is, by far, the biggest deal source in the world and, by far,

See Emerging markets, page 7

Senate health bill kills device tax, but tough sledding ahead

By Mark McCarty, Regulatory Editor

The Senate health care reform bill debuted to a waiting and somewhat hostile Washington and, as expected, the legislation retains the repeal of the tax on medical devices and diagnostics found in the House bill. The language in the Senate bill is seen as little more than a draft of what will eventually go to the Senate floor for a vote, however, a vote that most likely will be held under budget reconciliation rules.

The Republican Party has something of a tailwind in the form of several wins in special congressional elections over the past week, while President Trump has lowered his profile somewhat on Twitter. Still, Senate majority leader Mitch McConnell (R-Ky.) has indicated that he

See Senate, page 9

Regulatory front

Reminding President Donald Trump of his promises three months ago to get tough on drug prices, Reps. Elijah Cummings (D-Md.) and Peter Welch (D-Vt.) asked him to hold to the promises and back them with action. In a letter sent to the president Wednesday, the congressmen expressed concern over recent media reports indicating that a pending executive order on the issue comes straight from the biopharma industry's wish list. If that's the case, the lawmakers told Trump, it "would be a betrayal of the very people who supported you and rely on you to make good on your promises." The letter urged the president to direct the administration's internal working group on drug prices "to embrace the aggressive reform desperately needed by Americans . . . rather than the steps they are reportedly considering at the behest of the pharmaceutical industry."

Sen. Chuck Grassley (R-Iowa) elicited **FDA** Commissioner Scott Gottlieb's support for legislation intended to improve access to generic drugs in an effort to reduce drug prices. S. 974, the Creating and Restoring Equal Access to Equivalent Samples Act, includes provisions to deter brand companies from using risk evaluation and mitigation strategies (REMS) to deny generic firms access to drugs for bioequivalency studies and gives the FDA more flexibility in making single, shared REMS determinations. Grassley noted that a recent study found brand companies abuse the REMS program to block $5.4 billion in generic competition each year. The second bill the senator mentioned in a letter to Gottlieb is S. 124, the Preserve Access to Affordable Generics Act, which is intended to crack down on pay-for-delay patent settlements between brand and generic companies. In addition to his support for the two bills, Grassley asked Gottlieb to work with the Federal Trade Commission and the Justice Department to address anti-competitive behavior in the biopharma industry.

The U.S. **Patent and Trademark Office** (PTO) is extending the Cancer Immunotherapy Pilot Program, under which patent applications for cancer immunotherapies are granted special status and reviewed earlier. Since the program started on June 29, 2016, as part of the Cancer Moonshot, more than 80 petitions have been filed for participation in the program and nine patents have been granted, according to a notice slated for publication in Friday's *Federal Register*. Petitions have been submitted by various stakeholders from around the world, including independent inventors, universities, research institutions, hospitals, medical centers, government agencies, and large and small companies, the PTO said. Originally scheduled to end this month, the program is being extended through Dec. 31, 2018.

Financings

Argos Therapeutics Inc., of Durham, N.C., said it closed its $6 million private placement of a secured convertible promissory note with Pharmstandard International SA, the venture arm of Moscow-based **Pharmstandard**. Funds will be used to support continued development of rocapuldencel-T in metastatic renal cell carcinoma, including the pivotal phase III ADAPT trial, and for AGS-004 in HIV.

Clovis Oncology Inc., of Boulder, Colo., said underwriters of its recent public offering exercised in full their option to purchase an additional 511,363 shares, adding another $45 million to the $300 million offering. Stifel and Suntrust Robinson Humphrey are acting as co-managers. Clovis intends to use the net proceeds for general corporate purposes, including sales and marketing expenses associated with Rubraca (rucaparib) in the U.S. and, if approved by the EMA, in Europe, funding of its development programs, general and administrative expenses, acquisition or licensing of additional product candidates or businesses and working capital.

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Lynn Yoffee (News Director), Jennifer Boggs (Managing Editor), Peter Winter (*BioWorld Insight* Editor), Marie Powers (News Editor), Anette Breindl (Senior Science Editor), Mari Serebrov (Regulatory Editor), Amanda Lanier (Managing Editor), Karen Pihl-Carey (Analyst), Ann Duncan (Senior Production Editor)

Staff writers: Michael Fitzhugh, Randy Osborne, Shannon Ellis, John Fox, Brian Orelli, Nuala Moran, Cormac Sheridan, Alfred Romann, Tamra Sami

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Send all press releases and related information to newsdesk@bioworld.com.

Business office

Donald R. Johnston (Senior Director, Current Awareness), Penney Holland (Web Production Manager)

Contact us

Jennifer Boggs, (770) 810-3120 | Anette Breindl, (770) 810-3134 | Michael Fitzhugh, (770) 810-3064 | Penney Holland, (770) 810-3047 | Donald R. Johnston, (770) 810-3118 | Nuala Moran, 44-7778-868-579 | Randy Osborne, (770) 810-3139 | Marie Powers, (770) 810-3136 | Mari Serebrov, (770) 810-3141 | Cormac Sheridan, 353-87-6864323 | Peter Winter, (770) 810-3142 | Lynn Yoffee, (770) 810-3123

Personalized med

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Reilly spoke to an overflow crowd of about 300 attending a panel on the prospects of using I-O drugs as first-line therapy. He compared the progress of still-new therapies to plumbing. "The first time you buy a house and your sink breaks, you have to go and get the tools that are going to be used to fix that sink, you realize that, 'Oh, I have to go back to Home Depot or Lowe's again and again and again,'" he said, "It's a learning, iterative process."

Helping the personalized push is Altreca Inc., of Redwood City, Calif., which has found a way to measure and analyze the structure of clinically relevant immune responses, going on to identify the antibodies, T-cell receptors, and targets that can bring successful treatment outcomes. The company's Immune Repertoire Capture technology profiles a patient's immune response at the single-cell level by high-throughput means to provide "a complete picture of the ongoing immune response across time" as the patient undergoes treatment, said Altreca's Chief Scientific Officer Norman Greenberg. "Why would you rob a bank? Because that's where the money is. We're looking at patients who survived their cancers as a source of antibodies," he said.

Altreca has processed more than 150 "elite or exceptional responders," ransacking them for "antibodies and/or T cells that are responsible for their remarkable survival," Greenberg said. "It's the ultimate in personalized medicine – a patient's own antibodies, but now we're taking them out of the context, turning them into drugs, and we can put them into vials and treat multiple patients at pharmacologic doses."

The company has oncology and infectious-disease programs at the discovery stage. "Some of you are thinking, 'Great, we're probably identifying a lot of antibodies, neoepitopes, things that arise spontaneously and may not be generally expressed in the population,'" he said. "Let me tell you that a lot of the antibodies we're finding are in fact against public antigens." Patients are showing changes in B-cell and T-cell repertoires as they are given courses of I-O therapies.

Meanwhile, a "huge number of clinical trials" in the space are moving ahead, noted Kaan Certel, head of external innovation in oncology with Paris-based Sanofi SA. "We really need a rationale around how we're going to combine things, and currently, in the excitement of everybody wanting to be the first one to come up with the best combination, there really is no rationale out there," he said.

"Today, immunologists are saying, 'I told you so' to oncologists. Oncologists would say, 'Well, there have been targeted therapies and there have been chemotherapies that have worked in people before and in fact cured some people. What about strategies combining those targeted therapies [and chemotherapies] with I-O?'" But a grasp of the science is still lacking. "We now know that we don't understand the molecular basis of many of the cancers," he said. "We know that they are very diverse." Genome sequencing and data mining will solve some of the problems.

'Big, risky bet' in cancer vaccines

Another recent leg up is provided by reverse translation, said Kinney Horn, director of business development for Genentech, part of Basel, Switzerland-based Roche Holding AG. "We're actually seeing information coming out of the clinical trials, out of the patient experience, that is informing the research," he said. "The [animal] models are going to be there and, frankly, they're getting better and better. But what is different, maybe, over the last five years is that we're seeing information coming back that we can analyze from the human patients themselves. That is directing our research efforts. We have not quite seen anything like this before."

Moderating the panel was Tauseef Butt, president and CEO of Malvern, Pa.-based Progenra Inc., doing early stage research into the ubiquitin-proteasomal pathway and cellular protein regulation. The company has turned up candidate inhibitors of the ubiquitin pathway for potential use in cancer, inflammatory disease and other therapeutic areas.

An audience member asked how a startup company might be expected to put together the "incredibly expensive preclinical package" necessary to secure a deal with one of the major players working with I-O combos. Butt said "the science is really not very good, sorry, at small companies. 'Knock my socks off, give me the experiment.' I think that is what's being said" by panelists. But Sanofi's Certel said that "even failed trials are useful information."

Another audience member asked how exquisitely the mechanism of action must be known of a would-be drug, given that some are so complex. "I would say it's critical, to be honest with you," said BMS' Reilly. "Something that looks like it works but you don't actually understand how it works is far less useful" than more precise knowledge. "If you don't understand that, in my opinion, that's taking us back 20 years. We want to go forward."

Genentech's Horn pointed out that "drugs that are doing something to tumors are probably doing things to healthy cells, too." Having "mechanistic data and a bit of safety data" becomes particularly important in work with combos, he said, adding that his firm is often inspired to make deals based on "scientists getting excited about the mechanism" as they know it.

Asked about new modes in pipelines, Horn said his firm "made a very big bet, it's a risky bet" in Biontech AG, of Mainz, Germany, in September 2015, paying $310 million in up-front and near-term milestone payments. The deal is geared for developing cancer vaccines.

"We think that, if this does work, it would be the beginning of patients having their tumors sequenced, characterized at an individual level, and then a vaccine prepared just for them very quickly to be combined with a lot of the other marketed agents for a truly personalized approach to cancer," he said.

"We follow the science in everything we do, but I think going back to the individual patient is probably the path to above 30 percent [efficacy of I-O drugs among patient populations] to sustained cures." ♦

Advocacy

Continued from page 1

Not just any patient with Crohn's disease, cystic fibrosis, mitochondrial disease or melanoma, but for all people seeking a patient-centric public policy environment and for those working to advance drug development.

"So far this has been my favorite panel. You're up against former prime ministers," said Robert Coughlin, referring to British Prime Minister David Cameron's keynote address on Tuesday.

Coughlin, president and CEO of the Massachusetts Biotechnology Council, addressed the panel during the question-and-answer period of the Fireside Chat, titled "Understanding the Patient Voice: Three Unique Perspectives on Healthcare." The BIO convention will be held in Boston in 2018, so Coughlin asked, "How do we do more of this?"

The panel was led by Paul Hastings, chairman and CEO of Redwood City, Calif.-based Oncomed Pharmaceuticals Inc., who was diagnosed with Crohn's disease at age 13 and who runs a patient advocacy organization called Youth Rally. At least 70 other patient advocacy organizations are participating in the BIO conference. In 2016, 341 companies requested patient advocacy meetings at the convention, and those requests topped 400 this year, indicating an increasing interest in accessing advocacy funding and in incorporating patient voices into decision-making.

"Part of why I do what I do in biotech is for what I went through in my life as a patient. I bet everyone in this audience has been a patient," Hastings said. "I hope that none of us will forget that patients are the reason that we exist in the biotech and pharmaceutical industries."

Emily Kramer-Golinkoff, the co-founder of Emily's Entourage, is a 32-year-old woman who has the advanced stages of the fatal and genetic lung disease cystic fibrosis. She has a rare nonsense mutation and about 35 percent lung function. Every day is three to four hours of inhaled antibiotics and other treatments, including using an inflatable machine to help dislodge the mucus in her airways.

When she and her family saw no work was being done on her mutation, "we threw ourselves into the space really out of desperation," she said. Emily's Entourage has raised more than $2.5 million in an effort to catalyze drug discovery and development. "What's unique about our approach is we don't care how we get there," Kramer-Golinkoff said. "We're scrappy and agile and willing to do whatever it takes."

T.J. Sharpe started the Patient #1 blog to chronicle his fight with melanoma, which first appeared as stage I at age 25, but returned as stage IV 12 years later, resulting in a 16-day hospital stay and tumors in his lungs, liver and spleen.

"Problem was I had a 2-year-old daughter and a 4-year-old son," he said, and the doctor told his wife he had two years of life.

But two years was not good enough for Sharpe, who pursued both a tumor-infiltrating lymphocyte trial and an anti-PD-1 trial, and "I'm still here 4.5 years later" and getting his 73rd infusion on Friday.

> *"One thing I think about a lot is when you have a progressive disease, even just stability is a tremendous gift. For patients fighting progressive illnesses, the smallest gains can be unbelievably profound to us.*
>
> Emily Kramer-Golinkoff
> CF patient advocate.

His first clinical trial was held up by contract negotiations, but Sharpe "called the pharmaceutical company and told them they needed to sign the contract." While participating in the first trial, which failed to help him, he continued to search for other options.

"You need to be proactive in managing your diagnosis, insisting on getting the right answer from doctors," he said.

'We work for patients'

Liz Kennerley, a patient advocate for the United Mitochondrial Disease Foundation, meets with legislators on Capitol Hill to advocate for rare diseases. Speaking for others with mitochondrial disease helps lessen the personal blow she feels when someone dies or has a setback.

"It's been an emotional roller coaster. I can frown, roll my eyes, or throw things at the television," Kennerley said, "or I can change things for the better as best I can."

Part of the advocacy efforts made by the panelists include addressing the access to clinical trials, reducing the burden of prescription costs, and incentivizing researchers to tackle rare diseases and mutations, looking toward patients themselves for quality-of-life measurements.

"One thing I think about a lot is when you have a progressive disease, even just stability is a tremendous gift," said Kramer-Golinkoff. "For patients fighting progressive illnesses, the smallest gains can be unbelievably profound to us."

Like Hastings, Coughlin said he entered the biotech industry because of a disease that touched his own life, namely his 15-year-old son's cystic fibrosis.

Behind him during the Q&A, BIO's senior vice president for science policy, Kay Holcombe, said, "The most important things we can do as companies, as researchers, and most importantly as people, is to know our patients, and not just as examples of what went wrong with your genes."

Holcombe said a company where she once worked knew not only patients, but their families and kids, and the names of their kids. "We grew up in an environment where our CEO told us every single day in every single way that we work for patients because patients are people and we want to help them."

The company Holcombe referred to was Cambridge, Mass.-based Genzyme Corp., a champion for rare diseases that is now part of Sanofi SA. It was led by Henri Termeer, who passed away in May. (See *BioWorld Today*, May 16, 2017.) ♦

NIH

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Business Innovation Research (SBIR) grant program through fiscal year 2022.

There are grant opportunities for early stage startups, with $300,00 available for the first nine to 12 months, and then follow-on funding for up to $2 million for two years, Christie Canaria, program director and program lead of the National Cancer Institute (NCI) SBIR funding program, told a BIO 2017 panel.

A fast-track mechanism is another option that can be submitted simultaneously if a company has "great preliminary data," said Canaria, who is also program lead of the I-Corps program at the NIH. The I-Corps program, an intense entrepreneurial immersion course for scientists, is designed to help small companies get products out of the lab.

Roughly 50 percent of new companies will fail, and the "number one reason they fail is because they are creating something nobody wants," said Canaria. "I-Corps is designed to address that."

NIH also provides mentoring assistance to facilitate partnerships between awardees and funding partners.

NCI an 'investor'

Reflexion Medical is developing the first biology-guided radiotherapy system to treat cancer, and the NIH funded the company in the early stages of the process, said Reflexion Medical co-founder Sam Mazin. He said the company "considered NCI as an investor."

Reflexion built a machine to combine positron emission tomography (PET) with radiology. PET has changed how cancer is managed, and the industry is getter much better at diagnosing localized disease, resulting in longer survival, he said.

If radiation is added to the mix, it is possible to improve efficacy of systemic therapies, because radiation tends to be agnostic to the type of cancer, he said.

By using PET in a novel way, Reflexion's technology prompts tumors to "light up," guiding the radiation beam that then zaps the tumors immediately, he said.

NIH's SBIR program helped develop the guided radiotherapy system, and Reflexion is starting to assemble its first full system, which is expected to be commercialized in the next 18 months or so.

Reflexion received a phase I SBIR grant in 2011, as well as a phase II SBIR grant for $1.5 million in 2014.

Mazin said the grant was critical to help get Reflexion to proof of concept. He applied for the SBIR grant and seed funding at the same time, and it took about 18 to 20 months from the time he applied for the grant before the money came in.

He said SBIR helped to mitigate some of the technical risk, which helped de-risk the product for investors.

Following the SBIR grants, Reflexion closed a series A round for $11.6 million from Sofinnova Partners, Pfizer Venture Investments and Venrock. It then secured a $46 million series B round in July 2016 led by new investor KCK Group. Existing investors also participated.

Validation for VCs

The NCI relationship helped validate the technology, because it went through a peer review process, and that ended up being helpful in attracting private capital as well as academic and clinical collaborators, Mazin said.

His advice to other companies looking for NIH SBIR grants? Apply early, and work closely with the SBIR program officer. He said letters of support are helpful, too.

Offering the venture perspective was Arch Ventures principal Ari Nowacek, who gave an overview of Arch's strategy – get in early and co-lead a company it's investing in, with a seat on the board as well as co-development of the product.

With $2.5 billion under management, Arch will often seed a company for $100,000 and then come in with a series A of $5 million to $15 million. He said three-fourths of Arch's investments are life sciences companies.

"Public funding is good when it is available and nondistracting," Nowacek said, but if it's not properly aligned, it's not a good idea.

From an investor perspective, he said that going toward private funding is like buying equity in a product to see it built as quickly as possible.

Private investors need to see successful companies, he said. The technology is not enough, because investors want to see a unique technology coupled with protection, a solid product and a business model that will drive value to maximize return on investment. "If we don't make good calls, we go out of business," he said.

Public agencies like the NIH are investors as well, Nowacek said, stressing that if technology is de-risked, investors are more willing to invest

"When I look at a SBIR-funded group that's gone through phase II, I know it works," he said, "and I can take it to the team and focus on the business model." ♦

Financings

Proteon Therapeutics Inc., of Waltham, Mass., said it entered a securities purchase agreement with a syndicate of current and new investors, led by an affiliate of Deerfield Management, for the sale of 22,000 shares of the company's series A convertible preferred stock for gross proceeds of $22 million. Other participants in the financing include Abingworth, Fairmount Funds, Perceptive Advisors, Pharmstandard, RA Capital, Skyline Ventures, TVM Capital and certain other stockholders who invested prior to Proteon's IPO. Proceeds will be used to complete the ongoing PATENCY-2 trial testing vonapanitase in patients with chronic kidney disease undergoing surgical creation of a radiocephalic arteriovenous fistula for hemodialysis and to fund continued market access activities. The financing also extends the company's cash runway from the third quarter of 2018 into the fourth quarter of 2019.

Novartis

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inhibitor, Ilaris (canakinumab).

Basel, Switzerland-based Novartis said Thursday that Ilaris met the study's primary endpoint, a composite of heart attack, stroke and cardiovascular death. The implications of the study extend well beyond cardiovascular disease, however. The result appears to validate a much broader hypothesis, that tackling sterile inflammation can confer benefit in a chronic indication.

"This clearly puts the inflammatory process front and center," said Luke O'Neill, professor of biochemistry at Trinity College Dublin and co-founder and chief scientific officer of Dublin-based immunology startup Inflazome Ltd.

A clever patient selection strategy may have helped to uncover the drug's effects. The trial recruited about 10,000 patients who had suffered one heart attack and who had elevated levels of C-reactive protein, a commonly used marker of inflammation. "Those patients were inflamed," O'Neill said.

Although analyst reaction suggests expectations for a positive outcome were low, Novartis' decision several years ago to reduce the number of participants from 17,000 to 10,000 may have been a positive omen. "They must have had a very clear signal," O'Neill said. "It wouldn't surprise me if they're getting a readout in type 2 diabetes as well."

The Cantos trial included a subgroup of diabetes patients who were followed to see if the addition of Ilaris to standard of care improved insulin secretion and insulin sensitivity.

For now, the scientific community will have to wait to see the numbers. Novartis plans to present the full study data at a medical congress this year. "For me, the devil is going to be in the detail," O'Neill said.

Industry is likely to start mobilizing immediately. "Other companies will be jumping back into this again," he said. Several other firms had targeted the Il-1beta pathway without success in a major indication. Gevokizumab, an anti-IL-1beta antibody that Berkeley, Calif.-based Xoma Corp. originally developed and Suresnes, France-based Les Laboratoires Servier SAS in-licensed, failed a phase IIb trial in diabetes, for example. (See *BioWorld Today*, March 24, 2011, and July 23, 2015.)

"This was the last-chance saloon for the IL-1 business," he said.

The finding will also energize companies like Inflazome, which are focused on developing small-molecule inhibitors of the NLRP3 inflammasome, a protein complex that responds to danger signals or tissue injury by activating inflammation through the IL-1beta pathway, as well as through IL-18 and by initiating an independent signal cascade that leads to pyroptosis, a highly inflammatory form of programmed cell death. In cardiovascular disease settings, cholesterol deposition is considered to be the root cause of the inflammation. In gout, uric acid crystals are considered the culprit, while in obesity, the lipid species ceramide is the problem. In Alzheimer's disease, beta-amyloid deposition is the issue, whereas in Parkinson's disease, alpha-synuclein, a protein found in Lewy bodies, may be the problem.

> *"This was the last-chance saloon for the IL-1 business.*
>
> Luke O'Neill
> CSO, Inflazome Ltd.

Reimbursement path less clear

Ilaris gained its first FDA approval in June 2009. It is currently indicated for treating a number of rare diseases, including several IL-1beta-driven cryopyrin-associated periodic syndromes, as well as a form of juvenile arthritis and, in Europe only, gouty arthritis. First-quarter sales this year came to $82 million.

But an approval in a large indication, such as cardiovascular disease, could transform its prospects. Investors duly responded. Shares in Novartis (NYSE:NVS) were up by almost 4 percent by mid-afternoon Thursday, implying a gain in the company's valuation of more than $8 billion. The stock ended the day at $86.34, up $3.78.

"Cantos was a high-risk study, given there were no phase II data upon which to base expectations, and as a result expectations for success have been low," Jefferies analyst Jeffrey Holford stated in a research note. "However, there is a clear unmet need, with an estimated 7.29 million heart attacks globally, whilst people who have suffered a prior heart attack have a higher ongoing risk of having another event or dying, and in around four in 10 people this risk is directly related to increased inflammation associated with atherosclerosis," he added.

The clinical potential of Ilaris in cardiovascular disease looks promising, but a clear path to reimbursement is less so. The first two antibody-based therapies to gain approval in a cardiovascular indication, the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors Repatha (evolocumab) and Praluent (alirocumab), elicited significant levels of controversy. A monthly 150-mg dose of Ilaris is currently priced at about $16,000. Patients on the Cantos trial received quarterly injections of the drug at three doses, 50 mg, 150 mg and 300 mg. It is not clear which provided the greatest risk-benefit, but the present pricing model will need to be substantially revised if the drug is to have a significant level of uptake in cardiovascular disease.

Novartis struggled initially to gain reimbursement for another cardio drug, Entresto (sacubitril/valsartan), which gained approval in July 2015 for treating heart failure. That product is starting to gain momentum, however. Novartis reported $84 million in first-quarter sales this year, up from $17 million in the same quarter in 2016. ♦

Emerging markets

Continued from page 1

the leader in technologies. In order to make innovations global, we need to invest here," he said.

Companies have also reaped rewards from Russian trans-border financiers. Selecta Biosciences Inc., for example, drew a $25 million investment from the nanotechnology-focused Rusnano Group in 2011. Despite initial fears expressed by the company's board and U.S.-based venture investors at the time that Russia might seek to steal Selecta's intellectual property, they've been "a very good investor," said Werner Cautreels, Selecta's CEO and president. The relationship has been so strong that the Watertown, Mass.-based company still runs a wholly owned subsidiary, Selecta RUS, in the Moscow region where lab work on its HPV-associated cancers is underway.

Selecta's most recent 10-K report cautions investors about the possibility that its Russian subsidiary could be adversely affected if Russia were to take retaliatory action over U.S. sanctions tied to the Ukraine conflict. But asked by *BioWorld* whether the growing political complexity of U.S.-Russia relations has had any impact on Selecta, Cautreels said that it has not.

Panel moderator and University of Pennsylvania professor Stephen Sammut added that he believes "it is the province of life scientists and entrepreneurs, given the vitalness of the work that we do, to perhaps help guide our political leaders to [understand that] we are truly in a borderless world when it comes to health."

Ventureast, one of the first and oldest health care-focused venture capital firms in India, has sought to reap the benefits of that borderless landscape, investing in home health care, diabetes testing and other businesses seeking to meet growing global needs. "No matter where you live, the problems are accessibility, affordability and quality of care," said Bobba Venkatadri, a general partner in the firm who splits his time between San Francisco and Hyderabad.

Acknowledging what Sammut pointed out can be a sometimes exclusive "club" of big-name U.S. venture investors that tend to syndicate deals together to the exclusion of lesser-known foreign investors, Venkatadri also spoke to a solution for that problem: "What they're looking for is complementary skills. What do we bring to the party? What value do we bring to the business?"

For Ventureast, part of that value proposition turns on manufacturing. India has the highest number of FDA-approved manufacturing plants outside the U.S., putting Ventureast in a position to help facilitate more capital-efficient manufacturing, Venkatadri said. Prized access to the large population of treatment-naïve patients in India for clinical trials has also been a selling point, he said, though quality control issues have stood in the way of the country truly realizing that advantage in recent years. (See *BioWorld Today*, Feb. 9, 2017.)

Closing out the panel, Steven Wang, managing partner and founder of Shanghai-based Highlight Capital, gave voice to the benefit that a home team advantage can sometimes yield: "The regulatory space [in China] is complicated to understand. That creates an opportunity for VCs like ourselves to create a better return," he said.

> *"We think the U.S. is, by far, the biggest deal source in the world and, by far, the leader in technologies. In order to make innovations global, we need to invest here.*
>
> Alexey Konov
> CEO of RBV

No doubt, some of the seeds planted during BIO 2017 will lead to yet further opportunities for ex-U.S. investors. Russia alone sponsored the attendance of 14 biomedical startups from the Skolkovo Foundation, a nonprofit science and technology development center in the Moscow suburb of Skolkovo. As the panel met, representatives of some of those startups were in the midst of partnering talks, conversations that could set in motion events that might one day lead to solid exits for their backers. ♦

Regulatory front

The **FDA** is seeking comments on issues related to the continuous manufacturing of solid dosage drugs. In particular, the agency would like feedback on the science, technology and best practices discussed in the C-SOPS document the industry submitted last year. It also would like comments on already published recommendations regarding continuous manufacturing, including the regulatory and quality considerations that came out of a May 2014 symposium on the topic, according to a notice scheduled for publication in Friday's *Federal Register*. Comments may be submitted to the docket through Sept. 21.

Financings

Spring Bank Pharmaceuticals Inc., of Hopkinton, Mass., priced its public offering of about 2.9 million shares at $13 apiece for gross proceeds of about $37.5 million. Spring Bank has granted underwriters a 30-day option to purchase up to an additional 432,692 shares. Cantor Fitzgerald & Co. and William Blair & Co. LLC are acting as joint book-running managers, while Chardan is acting as co-manager for the offering, expected to close on or about June 27. Spring Bank intends to use the net proceeds for continued development of its product candidates and general corporate purposes.

Tapimmune Inc., of Jacksonville, Fla., said it entered definitive subscription agreements to raise aggregate gross proceeds of about $6.82 million in a private placement transaction with accredited investors and from the exercise of certain outstanding series E warrants by certain existing institutional investors. The closings of the transactions are subject to delivery of funds from the investors and are expected to occur on June 26. Tapimmune expects to use the net proceeds for general corporate purposes, including clinical trial expenses and research and development expenses over the next 18 months. Katalyst Securities served as the placement agent.

Repare

Continued from page 1

novel targets identified through CRISPR-based induction and screening of mutations that give rise to synthetic lethality.

Repare was jointly founded by Daniel Durocher and Frank Sicheri, both of the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital in Toronto, and Agnel Sfeir, of Skirball Institute of Biomolecular Medicine, NYU Langone Medical Center in New York. Founding investor Versant Ventures incubated the fledgling firm and helped conduct some of the early research at its Highline and Blueline facilities, located in New York and Toronto, respectively.

San Francisco-based Versant and Cambridge, Mass.-based MPM Capital co-led the series A round. Other participants included Montreal-based FTQ, the Celgene Switzerland LLC affiliate of Summit, N.J.-based Celgene Corp., and Montreal-based BDC Ventures.

The advent of poly (ADP-ribose) polymerase (PARP) inhibitors for treating BRCA-mutated cancers has validated the general concept of identifying a cancer's Achilles heel by uncovering hidden dependencies between pairs of genes. Mutations in either BRCA1 or BRCA2 – which are risk factors for hereditary forms of breast cancer and ovarian cancer – compromise cells' ability to repair DNA damage. PARP inhibition exploits that vulnerability by knocking out an alternative DNA repair mechanism.

Historically, a lot of the early work on synthetic lethality was conducted in yeast. Genes involved in DNA damage repair and cell cycle regulation represent the richest area to mine, Jerel Davis, managing director at San Francisco-based Versant, told *BioWorld*. "A lot of those genes have human orthologs, which are preserved over hundreds of millions of years."

Durocher, said Davis, had developed a "pseudo-industrial" platform employing CRISPR guide RNAs to create a genomewide library of knockouts that could be screened to identify hitherto unidentified dependencies between pairs of genes. It involves the de novo creation of cell lines incorporating a cancer-associated genetic lesion, which can then be subjected to genomewide knockouts in order to identify novel synthetically lethal mutations.

"We're not just using inference to understand the interaction based on cell profiling," Davis said. "It's a much more purist approach to understand synthetic lethal interactions."

Repare CEO Lloyd Segal, who joined Versant a year ago as entrepreneur in residence, built up a team that has translated the basic platform to an industrial setting. "What we have now is a platform that is highly validated and operates at a scale which, as far as I'm aware, is unmatched," he told *BioWorld*. The company has several drug discovery programs underway but is, for now, identifying just one. Its lead program involves inhibition of DNA polymerase theta (PolQ). Sfeir's lab recently identified its role in promoting alternative nonhomologous end-joining (alt-NHEJ), an essential DNA repair mechanism in cells that are compromised for homologous DNA repair. "It's a BRCA1 synthetic lethal partner," Segal said.

Repare is also working on synthetic lethal targets that go beyond the BRCA paradigm. "We have a really robust list that is driven by our proprietary biology and our clinical genetics database," Segal said.

The Repare team has also generated new mechanistic insights on clinical-stage drug programs whose developers may not fully appreciate their precise workings. "It's a truly important point about the unique capabilities of our platform," Segal said. "That is a non-trivial observation, one with a lot of business development opportunity for us."

The company also has in-house medicinal chemistry capabilities, led by vice president of discovery Cameron Black.

Artios Pharma Ltd., of Cambridge, U.K., which took in about $33 million in 2016 to focus on targets associated with DNA damage repair, is also working on PolQ. The company's leadership team includes some of those who steered the development of the first PARP inhibitor, Lynparza (olaparib), at Kudos Bioscience Ltd., which London-based Astrazeneca plc acquired more than a decade ago.

Versant's interest in the area of synthetic lethality was aroused by having "a front row seat" as an early investor in Boulder, Colo.-based Clovis Oncology Inc., Davis told *BioWorld*. Clovis developed PARP inhibitor Rubraca (rucaparib), which gained FDA approval in advanced BRCA-mutated ovarian cancer as a third-line therapy last December and which is on-course for approval in a broader patient population following the release of positive phase III data earlier this week. (See *BioWorld Today*, June 20, 2017.)

Others at play in the space include Ideaya Biosciences Inc., of South San Francisco, which raised $46 million in May last year to take forward a CRISPR-based platform for identifying new targets that mediate synthetic lethality in cancer. Cambridge, Mass.-based Tango Therapeutics Inc. took in $55 million in March this year to pursue a similar goal. Metabomed Ltd., of Yavne, Israel, raised $18 million in a series A round last year to pursue a systems biology-based approach to identifying synthetically lethal mutations.

Versant's Davis and MPM's Todd Foley are joining the Repare board. Its scientific advisory board includes: Samuel Aparicio, of the University of British Columbia, Vancouver; Jim Carmichael, of Celgene; Ronny Drapkin, of the University of Pennsylvania, Philadelphia; Laurie Glimcher, of the Dana-Farber Cancer Institute and Harvard Medical School; Mark Pegram, of Stanford University, of Stanford, Calif.; and Richard Wood, of the University of Texas MD Anderson Cancer Center, in Houston.

Repare's financing is the largest disclosed series A investment to close so far this year, according to BioWorld Snapshots. Although Kiniksa Pharmaceuticals, of Hamilton, Bermuda, unveiled an $80 million A round in January, that deal was actually completed in 2016. ♦

Senate

Continued from page 1

would like to see a finished bill on the Senate floor for a vote by July 4, leaving drafters of the legislation little time to make the changes needed to ensure the legislation can get to 50 votes. Some observers believe that a more realistic timeline for a vote on the bill is later in the month of July, with the August recess serving as a hard deadline for the vote.

The Republican Party has 52 seats in the Senate, and Senate budget reconciliation rules allows passage with only 51 votes. Should the Senate health care reform bill fail to garner more than 50 votes, Vice President Mike Pence would presumably cast the deciding vote.

The repeal of the medical device tax is hardly controversial – a sense-of-the-Senate vote affirmed the notion by a margin of 79-20 in March 2013 – and that legislation would put an end to the tax at the end of this calendar year, when the current two-year suspension of the tax terminates. Similarly, the excise tax on prescription drugs that was found in the ACA would no longer be in force in January 2018. Broadly speaking, the Senate bill would eliminate all the taxes imposed by the ACA with the exception of the so-called Cadillac tax on high-end health care plans offered by employers.

The Senate bill takes a $2 billion, one-year swipe at the opioid abuse problem, which would fund grants to the states via the Department of Health and Human Services in 2018. The monies could be used to fund treatment and recovery support services, and those with both mental health and substance abuse disorders would be eligible.

One feature of the Senate bill that could prove problematic for some conservatives is that it reduces the eligibility for health insurance exchange subsidies to 350 percent of the federal poverty level, a relatively small change from the 400 percent set point in the Affordable Care Act. On the other hand, those living below the poverty level in states that did not sign on for Medicaid expansion under the ACA would be eligible for subsidies, which ensures some GOP votes.

Generally speaking, federal spending on Medicaid would be pegged to the overall Consumer Price Index rather than the typically more generous medical price index under the Senate's first draft. One of the more interesting aspects of the Senate bill is that it does not seem to excise the Independent Payment Advisory Board, a feature of the Affordable Care Act that drew bipartisan fire even before passage.

The Senate bill retains a few features of the Affordable Care Act that would help keep some Republicans on board, including the provision that allows young adults to stay on their parents' health plans to the age of 26. On the other hand, the Senate bill makes funds available to stabilize the health insurance exchanges set up by the Affordable Care Act via $15 billion annually in 2018 and 2019, a sum that would drop by a third in the two following years. The roll-back of federal Medicaid funding to pre-ACA levels is a feature that will undoubtedly prove insuperable for any Senate Democrats who might otherwise have been willing to cross party lines to vote for the measure.

As might be expected, not all Senate Republicans are on board with the first draft of the legislation. Sen. Rand Paul (Ky.) has proposed legislation that would stipulate that a bill not be eligible for a vote on the Senate floor until one day has passed for each 20 pages taken up by that legislation. Paul said he would not vote for the Senate health reform bill in its current form, stating that while "the current bill does not repeal Obamacare. . . . I remain open to negotiations." Other members of the Senate GOP who have openly voiced concerns include Sens. Ted Cruz of Texas and Mike Lee of Utah.

Senate minority leader Chuck Schumer (D-N.Y.) said the Senate bill "is a wolf in sheep's clothing, only this wolf has sharper teeth than the House bill." Seema Verma, administrator of the Centers for Medicare & Medicaid Services, said in a June 22 statement that the ACA "is in a death spiral," and that Congress "must act now to achieve the President's goal to make sure all Americans have access to quality, affordable coverage." ♦

Other news to note

Angion Biomedica Corp., of Uniondale, N.Y., said it signed an exclusive license with **Elexopharm GmbH**, of Saarbrücken, Germany, for compounds that target aldosterone synthase (CYP11B2), a cytochrome P450 enzyme involved in the generation of aldosterone. Terms were not disclosed.

Eisai Co. Ltd., of Tokyo, and **Ewopharma AG**, of Schaffhausen, Switzerland, inked a deal in which Ewopharma acquired rights to commercialize several Eisai products in 11 countries in Central and Eastern Europe. Ewopharma will commercialize Halaven (eribulin mesylate) in nine countries within the EU and in two countries outside of the EU and will also commercialize Targretin (bexarotene) in Hungary and Poland as well as Zonegran (zonisamide) in Hungary. Ewopharma will be responsible for all aspects of pricing, reimbursement, marketing and distribution. Eisai will supply product and also provide significant product training and support across the relevant brands. Specific financial terms were not disclosed.

Invent Farma/Neuraxpharm Group, of Barcelona, Spain, acquired **FB Health SpA**, an Italian specialty pharma focused on neurology and psychiatry. Terms were not disclosed.

Kamada Ltd., of Rehovot, Israel, said it withdrew its marketing authorization application (MAA) for inhaled alpha-1 antitrypsin (AAT) therapy for the treatment of alpha-1 antitrypsin deficiency (AATD) with the EMA. Following extensive discussions with the EMA during recent months, Kamada said it concluded that the agency does not view the data submitted to date as sufficient for approval of the MAA, and that the supplementary data needed for approval requires an additional clinical trial. Kamada is currently in advanced discussions with the FDA in order to secure the approval of an IND this year to conduct a U.S. phase III pivotal study of inhaled AAT for the treatment of AATD that would begin in 2018.

Regulatory front

In a bipartisan effort, four senators introduced the STRONGER Patents Act to protect and support innovators and ensure that the U.S. patent system protects the intellectual property rights of inventors. The bill is intended to restore investor confidence in patents by ensuring that the new PTO administrative reviews are balanced and efficient. To restore incentives for parties to reach license agreements without going to court, the bill would re-establish that patents are property rights, enforceable with injunctions. It also would help universities and small businesses access the patent system and ensure that the PTO has unfettered access to the fees it collects so it can modernize its technology and issue patents of the highest quality.
The legislation is sponsored by Sens. Chris Coons (D-Del.), Tom Cotton (R-Ark.), Dick Durbin (D-Ill.) and Mazie Hirono (D-Hawaii).

Reps. Maxine Waters (D-Calif.) and Chris Smith (R-N.J.), co-chairs of the **Congressional Task Force on Alzheimer's Disease**, introduced a bill requiring the U.S. Postal Service to issue a semipostal stamp, with the proceeds going to fund Alzheimer's research at the **NIH**. Modeled on the breast cancer research stamp, the new stamp would raise public awareness about the disease and encourage voluntary contributions to research efforts, Waters said.

More than a quarter of adults surveyed said they would immediately stop taking a prescription drug, without consulting their doctor, if they saw an ad from a lawyer alerting the public about lawsuits against that drug. Fifty-three percent said they are personally concerned after seeing an ad about a drug they currently take, and 59 percent said they would call their doctor after seeing such an ad. **Public Opinion Strategies** conducted the online survey last month to assess how trial lawyer advertising regarding prescription drugs affects the broader public, as well as those taking the drugs mentioned in the ads. The survey was conducted among 1,025 adults throughout the U.S., along with 500 interviews with adults who indicated they are or had taken at least one of the following drugs or their generics: Actos (pioglitazone), Avandia (rosiglitazone), Crestor (rosuvastatin), Granuflo, Nexium (esomeprazole), Paxil (paroxetine), Pradaxa (dabigatran), Prozac (fluoxetine), testosterone, Xarelto (rivaroxaban), Yax/Yasmon/Ocella (drospirenone, ethinyl estradiol) and Zoloft (sertraline).

Other news to note

Nemus Bioscience Inc., of Costa Mesa, Calif., said tetrahydrocannabinol (THC) derived from NB-1111, a prodrug of THC, was able to concentrate in multiple compartments of the eye that correlated with the lowering of intraocular pressure in a normotensive ocular rabbit model. Native THC alone was unable to achieve concentrations in the eye comparable to NB-1111 under similar testing. Data from the preclinical experiments will be presented at the 27th Annual Symposium of the International Cannabinoid Research Society.

Psivida Corp., of Watertown, Mass., said it submitted a marketing authorization application to the EMA for Durasert, its three-year treatment for posterior segment uveitis. The filing was based on data from two phase III trials showing that Durasert achieved the primary endpoint at six months ($p < 0.001$), and the safety profile was comparable to the safety profile of existing steroid uveitis treatments.

Reata Pharmaceuticals Inc., of Irving, Texas, said the FDA granted orphan designation to omaveloxolone for the treatment of Friedreich's ataxia (FA). Omaveloxolone, a synthetic triterpenoid compound, demonstrated promising data earlier this month in part one of a phase II trial, showing that it induced Nrf2, which is suppressed in FA patients, and was associated with improvements in mitochondrial and neurological function.

In the clinic

AB Science SA, of Paris, reported data analyses from its phase III trial of masitinib in severe systemic mastocytosis at the International 22nd Congress of the European Hematology Association in Madrid, Spain. Masitinib, a tyrosine kinase inhibitor, showed a significant improvement over placebo according to its pre-specified primary endpoint, with a cumulative response of 18.7 percent vs. 7.4 percent, respectively (p=0.008). The primary endpoint was based on repeated measures methodology for rare diseases via the generalized estimating equation model, an established technique that makes a longitudinal analysis with respect to symptoms as opposed to the more conventional patient response rate at a single timepoint. Computing treatment effect according to cumulative response per patient confirmed the outcome on the primary endpoint: 26.7 percent vs. 12.8 percent, respectively (p=0.0212). Computing treatment effect according to individual patient response (Pearson chi-square) was also significant for masitinib: 40.3 percent vs. 24.2 percent, respectively (p=0.0062). Response per patient on all severe baseline symptoms for at least one visit was: 16.4 percent for masitinib vs. 1.6 percent for placebo (p=0.0062).

Alzheon Inc., of Framingham Mass., said a subanalysis of data from two phase III trials testing amyloid-targeted drug tramiprosate in 2,025 patients with Alzheimer's disease (AD) were published in *The Journal of the Prevention of Alzheimer's Disease*. Tramiprosate produced the largest efficacy signals in AD patients who were APOE4/4 homozygous with the mild form of the disease, as measured by ADAS-cog11, CDR-SB and the Disability assessment for dementia. Alzheon is currently developing ALZ-801, an optimized oral prodrug of tramiprosate that has improved gastrointestinal tolerability, with plans to run a pivotal trial in patients who are APOE4/4 homozygous with mild AD.

Ampio Pharmaceuticals Inc., of Englewood, Colo., said the first patient was dosed in its phase III AP-003-C study testing Ampion in Kellgren-Lawrence grade IV osteoarthritis of the knee. The 171-patient trial will compare Ampion to a saline control, measuring responder status using the Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International scenario D, a composite endpoint of various Western Ontario and McMaster Universities Osteoarthritis Index scores as well as the Physician Global Assessment scale.

Biopharmx Corp., of Menlo Park, Calif., said data of a previously disclosed phase IIb trial testing BPX-01, a topical hydrophilic gel formulation of the antibiotic minocycline, in patients with acne vulgaris will be presented at the Alabama Dermatology Society's Summer Symposium. In the trial, BPX-01 reduced acne lesions in subjects by 59 percent, compared to 44 percent for placebo, and BPX-01 produced at least a two-grade reduction in investigator global assessment with clear to almost clear in 25 percent of patients.

Braeburn Pharmaceuticals Inc., of Princeton, N.J., said phase II data demonstrated that long-acting buprenorphine (CAM-2038), a subcutaneous buprenorphine depot formulation, produces an immediate and sustained blockade of opioid effects and suppression of withdrawal symptoms in adults with opioid use disorder. Data were presented at the College on Problems of Drug Dependence meeting in Montreal and published in *JAMA Psychiatry*. The opioid challenge study, a double-blind, randomized, in-patient study involving 47 adults with moderate to severe opioid use disorder, attained the primary endpoint for both arms of CAM-2038 dosing levels by producing an immediate and sustained blockade of hydromorphone effects (liking maximum effect, 24 mg, 0.813; p<0.001, and 32 mg 0.753; p<0.001) and suppression of withdrawal (Clinical Opiate Withdrawal Scale, 24 mg 0.617; p<0.001, and 32 mg 0.751: p<0.001). CAM-2038 produced a rapid rise of buprenorphine in plasma with maximum concentration around 24 hours, with an apparent half-life of four to five days, and about 50 percent accumulation of tough concentration from first to second dose.

Delmar Pharmaceuticals Inc., of Vancouver, British Columbia, said it received institutional review board approval to conduct its pivotal phase III trial testing VAL-083 in patients with glioblastoma multiforme (GBM) whose disease has progressed following prior treatment with temozolomide and Avastin (bevacizumab, Roche Holding AG). The 180-patient trial, dubbed Study in Temozolomide-Avastin Recurrent GBM (STAR-3), will compare VAL-083 to investigator's choice salvage therapy with overall survival as the primary endpoint.

Devonian Health Group Inc., of Quebec City, said it plans to begin a phase IIa study of its lead product candidate, Thykamine, in patients with mild to moderate atopic dermatitis at the end of the month. The trial will enroll 92 patients who will receive one of three concentrations of Thykamine cream or placebo applied twice daily for 28 days. Thykamine, which was developed using Devonian's Supra Molecular Complex Extraction and Stabilisation Technology (SUPREX), is also in development as a treatment for ulcerative colitis.

Durect Corp., of Cupertino, Calif., said it completed enrollment in Persist, its pivotal phase III trial testing Posimir (SABER-bupivacaine) in patients undergoing cholecystectomy (gallbladder removal) surgery. Part one of Persist enrolled 92 patients who received either Posimir or placebo, and part two – added under advice from the FDA – will compare Posimir to standard bupivacaine HCl in 296 patients with a primary endpoint of pain reduction on movement from 0-48 hours after surgery. Posimir, which was recently licensed by the Sandoz AG division, of **Novartis AG**, of Basel, Switzerland, uses Durect's Sucrose Acetate isoButyrate Extended Release (SABER) technology to continuously deliver bupivacaine to the surgical site for 72 hours. (See *BioWorld Today*, April 11, 2016.)

Other news to note

Recce Ltd., of Sydney, said it completed construction of a production facility in Macquarie Park, with expected outputs capable of supporting antibiotic candidate Recce 327 through phase I and II testing.

Other news to note

Regeneron Pharmaceuticals Inc., of Tarrytown, N.Y. provided details on its 2009 agreement with Basel, Switzerland-based **Novartis AG** for anti-IL1beta antibody Ilaris (canakinumab) in which Regeneron receives a royalty on worldwide net sales of Ilaris that starts at 4 percent and reaches 15 percent when Ilaris annual sales exceed $1.5 billion. The royalty includes any future indications, including a potential label expansion from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) results reported by Novartis.

Roche Holding AG, of Basel, Switzerland, said its Genentech unit received FDA approval for Rituxan Hycela (rituximab and hyaluronidase human) for subcutaneous injection for the treatment of adults with previously untreated and relapsed or refractory follicular lymphoma, previously untreated diffuse large B-cell lymphoma (DLBCL) and previously untreated and previously treated chronic lymphocytic leukemia (CLL). The new treatment includes the same monoclonal antibody as intravenous Rituxan in combination with hyaluronidase human, an enzyme that helps to deliver rituximab under the skin, reducing administration time from 1.5 hours or longer to five to seven minutes. The hyaluronidase human component was developed by **Halozyme Therapeutics Inc.**, of San Diego.

Santhera Pharmaceuticals AG, of Liestal, Switzerland, said the U.K.'s Medicines and Healthcare products Regulatory Agency granted Raxone (idebenone) a positive scientific opinion through the Early Access to Medicines Scheme for Duchenne muscular dystrophy (DMD) patients with respiratory function decline not taking glucocorticoids. Santhera has filed an marketing authorization application in the EU and Switzerland for DMD patients with respiratory function decline who are not taking glucocorticoids.

Shire plc, of Dublin, said the EMA validated its MAA for Veyvondi (von Willebrand factor) to prevent and treat bleeding episodes and perioperative bleeding in adults (ages 18 and older) diagnosed with von Willebrand disease, an inherited bleeding disorder. The EMA filing is based on data from two phase III trials. Veyvondi was approved by the FDA in 2015. (See *BioWorld Today*, Dec. 10, 2015.)

Zogenix Inc., of Emeryville, Calif., said the FDA granted orphan drug designation to ZX-008 (low-dose fenfluramine) for the treatment of Lennox Gastaut syndrome (LGS), a type of childhood-onset epilepsy. Earlier this year, the EMA gave ZX-008 orphan designation for the treatment of LGS. ZX-008 is currently being tested in a phase III study in Dravet syndrome, another type of infant-onset epilepsy for which Zogenix also has U.S. and EU orphan designation, with top-line data expected in the third quarter of 2017.

In the clinic

Hutchison China Meditech Ltd. (Chi-Med), of Hong Kong, said the first patient was dosed in a phase I/II trial of HMPL 453, a small-molecule inhibitor targeting fibroblast growth factor receptor (FGFR), in China. The phase I portion will evaluate HMPL 453 in a dose-escalation stage that will enroll patients with locally advanced or metastatic solid tumors, for whom standard therapy either does not exist or has proved to be ineffective or intolerable, regardless of genetic status, to determine the maximum tolerated dose and recommended phase II dose (PR2D). The phase II portion will measure objective response rate at the RP2D as the primary endpoint in patients with FGFR dysregulated tumors, including advanced bladder cancer, advanced cholangiocarcinoma and other solid tumors. The study in China will complement the first-in-human phase I trial in Australia that started earlier this year.

Ionis Pharmaceuticals Inc., of Carlsbad, Calif., said it completed enrollment in the phase I/IIa trial of IONIS-HTTRx in patients with Huntington's disease. Ionis plans to report top-line results around the end of this year. Ionis plans to begin an open-label extension study in the next several months for patients who complete the phase I/IIa study. IONIS-HTTRx, which is partnered with Basel, Switzerland-based **Roche Holding AG**, is an antisense drug designed to reduce the production of the toxic mutant huntingtin gene that's linked to Huntington's disease.

Otonomy Inc., of San Diego, said it successfully completed an end-of-phase II review with the FDA for Otiprio (ciprofloxacin otic suspension) as a treatment for pediatric patients with acute otitis media with tympanostomy tubes (AOMT). Based on advice from the FDA during the meeting, Otonomy plans to conduct a single, sham-controlled, phase III trial of approximately 200 pediatric patients with AOMT to support approval of Otiprio for that indication. Timing for the start of the trial hasn't been determined. A phase II trial testing Otiprio in 95 pediatric patients with unilateral or bilateral AOMT demonstrated that both doses of Otiprio were well-tolerated and achieved higher and statistically significant clinical cure rates over sham treatment.

Summit Therapeutics plc, of Oxford, U.K., presented data from two phase I trials of ezutromid, Summit's lead utrophin modulator, in patients with Duchenne muscular dystrophy (DMD) at the European Paediatric Neurology Society Congress in Lyon, France. The oral presentation focused on how formulation changes and dietary advice increased ezutromid exposure in patients. An ongoing phase II trial, PhaseOut DMD, is utilizing both methods to measure the impact of ezutromid drug exposure on pharmacology, safety and efficacy with longer term dosing of patients with DMD.

Zealand Pharma A/S, of Copenhagen, Denmark, and Boston-based **Beta Bionics Inc.** reported positive safety data from a phase IIa trial testing Zealand's dasiglucagon, a glucagon analogue, in Beta Bionics' iLet dual-hormone artificial pancreas system in 10 adult patients with type 1 diabetes. Under challenging conditions with basal rate of insulin up to twice the normal rate, the artificial pancreas system was able to keep glucose levels in the range of 70 mg/dL to180 mg/dL approximately 70 percent of the time when dasiglucagon was used in the system and 65 percent of the time when recombinant glucagon was used. No severe hypoglycemic episodes were observed, and the time below 60 mg/dL glucose was approximately 13 percent for dasiglucagon and approximately 18 percent for recombinant glucagon. The companies plan to move forward with a pivotal registration trial to support approval of the iLet bionic pancreas delivering both insulin and dasiglucagon.