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WORLD STEM CELLS & REGENERATIVE MEDICINE

Panelists: Positives amid setbacks in cell therapy, regenerative medicine space

By Nuala Moran, Staff Writer

LONDON – There are storm clouds on the horizon for cell therapy and regenerative medicine, with a number of trial failures in the past few weeks and the mounting problems in getting reimbursement for high-cost products that are edging to market, adding to the huge scientific and development challenges that the sector faces.

Recent news has included negative data in Athersy Inc.'s phase II trial of its allogeneic cell therapy in ulcerative colitis, announced April 29, and Cytomedix Inc.'s May 5 decision to ax its Aldagen subsidiary after its autologous stem cell therapy failed in a

See Stem cells, page 3

SUCCESS FOR SUPPRESS?

Chimerix raises $103M for brincidofovir push; potential use widens

By Randy Osborne, Staff Writer

More than half the gross proceeds of Chimerix Inc.'s $103.8 million from a public offering will go toward advancing the oral nucleotide analogue lipid-conjugate drug brincidofovir, the company said in its 424B5 filing with the

See Chimerix, page 4

IN THE CLINIC

Voltarra seeks 'lightning' strike with zoledronic acid derivative in knee OA

By Marie Powers, Staff Writer

Launched last year with a portfolio of early stage small molecules and late-stage clinical assets assembled through a pair of acquisitions, Voltarra Pharmaceuticals Inc. has moved like

See Voltarra, page 5

FINANCINGS

Lysogene raises $23M for Sanfilippo syndrome A gene therapy

By Cormac Sheridan, Staff Writer

Lysogene SAS raised €16.5 million (US$22.6 million) in a series A round to continue its clinical development of SAF-301, a gene therapy treatment for Sanfilippo syndrome type A, a rare

See Lysogene, page 6

REGULATORY FRONT

States signal on 'right to try': Washington, we have a problem

By Mari Serebrov, Washington Roundup

Sending a clear signal to Washington, Louisiana is poised to become the second state to enact a law recognizing the right of terminally ill patients, who have run out of options, to try investigational

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THE BIOWORLD BIOME

Keeping insulin around

By Anette Breindl, Science Editor

Logic suggests that raising insulin levels through stabilizing insulin should lead to improved glucose control. But in practice, mice lacking IDE, the enzyme that degrades insulin, have impaired glucose control.

Now scientists from Harvard University have developed a pharmacological IDE

See Insulin, page 8

NEWCO NEWS

Recent start-up Cour lands former Pfizer R&D chief as chairman

By Michael Fitzhugh, Staff Writer

Cour Pharmaceutical Development Co. Inc., a small company developing nanotechnology-based immunotherapies for acute inflammation and autoimmune disease, has appointed Pfizer R&D

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OTHER NEWS TO NOTE

Adamas Pharmaceuticals Inc., of Emeryville, Calif., received a $25 million milestone payment from **Forest Laboratories Holdings Ltd.**, of New York, following the FDA's acceptance of the new drug application for MDX-8704, a fixed-dose combination of memantine HCl extended-release capsules and donepezil HCl, in development as a once-daily therapy to treat moderate to severe dementia of the Alzheimer's type in the U.S. The companies are collaborating on the development of MDX-8704, for which Forest holds exclusive U.S. commercialization rights. (See *BioWorld Today*, March 5, 2014.)

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., said preclinical results using RNAi therapeutics targeting aminolevulinic acid synthase-1 (ALAS-1) to treat hepatic porphyrias, including acute intermittent porphyria (AIP), were published in the *Proceedings of the National Academy of Sciences*. In the paper, Alnylam scientists and collaborators at the Icahn School of Medicine at Mount Sinai in New York documented results from a mouse model of AIP showing that RNAi therapeutics targeting ALAS-1 can completely block the abnormal production of toxic intermediates of the heme biosynthesis pathway that cause the symptoms and disease pathology of AIP. In addition, preliminary comparative studies showed that ALAS-1 siRNA administration was more effective than heme administration in the treatment of an acute attack. The paper provides proof of concept for an RNAi therapeutic to treat AIP, according to the company, which said it is advancing its development candidate, ALN-AS1, designed to knock down ALAS-1, and expects to file an investigational new drug application by early next year.

Antiop Inc., of Lexington, Ky., has signed an agreement to work with **Reckitt Benckiser Pharmaceuticals Inc.**, of Richmond, Va., to accelerate production and worldwide marketing of intranasal naloxone, its drug for treating opioid overdose. Reckitt Benckiser and Antiop will co-develop the nasal naloxone spray, which is entering its final trial in June, through potential FDA approval. Antiop CEO Daniel Wermeling said he is confident the company will meet eligibility requirements for FDA priority review after the company's new drug application is filed.

Cognition Therapeutics Inc., of Pittsburgh, said its small-molecule Abeta receptor agonist program for Alzheimer's disease was selected for funding by the National Institute on Aging NIH Alzheimer's Disease Development Program. The cooperative agreement program will provide the firm with an estimated $1.4 million in funding over four years to support critical drug development activities aimed at securing investigational new drug status.

Cytokinetics Inc., of South San Francisco, highlighted three recently published manuscripts detailing tests of tirasemtiv, its skeletal muscle activator and the lead candidate in its skeletal muscle contractility program. The papers, published in *PLOS ONE*, *Muscle & Nerve*, and the *American Journal of Respiratory and Critical Care Medicine*, described positive early stage data related to tirasemtiv's impact on a mouse model, dosing in a phase I first-in-human trial, and whether a structural analogue of tirasemtiv could improve contractile weakness of diaphragm muscle fibers that develops in mechanically ventilated critically ill patients.

Edison Pharmaceuticals Inc., of Mountain View, Calif., said Japanese regulators granted orphan status to EPI-743 for the treatment of Leigh syndrome. The drug, a small-molecule para-benzoquinone designed to augment endogenous glutathione biosynthesis, is in phase IIb testing in children with the inherited neuromuscular disorder in the U.S., and a phase IIb/III trial is being conducted in Japan in conjunction with **Dainippon Sumitomo Pharma Co. Ltd.**, of Osaka, Japan.

STOCK MOVERS 5/21/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$14.71	+0.62%
Bluebird Bio	-$3.96	-14.55%
Chimerix Inc.	+$1.98	+13.92%
La Jolla Pharmaceuticals	-$0.97	-11.32%

Biotechs showing significant stock changes Wednesday

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Stem cells

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stroke trial. But does that mean the sector is in trouble?

Not according to Greg Bonfiglio, managing partner of Proteus Venture Partners. "I think the field is progressing very nicely," he told *BioWorld Today*, calling recent events "a natural correction" to a space that "as a whole, is doing quite well."

Bonfiglio posed the question during a panel convened to discuss the state of the industry at this week's World Stem Cells & Regenerative Medicine meeting: "Is it a natural downtick, or is it an ominous sign something not good is going to happen?" he asked.

For Alain Vertes, managing director of Nxr Biotechnologies, who was head of F. Hoffman-La Roche Ltd.'s regenerative medicines unit at the point the pharma decided to quit the field, the current problems are a "small accident." Looking to history, for example, 15 of the first 16 clinical studies of cell therapies failed.

"It couldn't have been worse; what we are seeing now is nothing in comparison," he said. The fundamentals of the sector are strong, and there is increasing understanding of the basics of the technology.

The value of Athersys' shares halved when the negative data from the trial of its off-the-shelf stem cell product partnered with Pfizer Inc. were published. (See *BioWorld Today*, April 29, 2014.)

However, Tim Allsopp, head of external research in regenerative medicines at Pfizer's Neusentis R&D unit in Cambridge, UK, said the program is still alive. "It's an ongoing collaboration. We still believe in the partnership, and it was a pretty well designed trial," Allsopp said. The treatment was safe and well tolerated.

The current position is "quite positive" even though there was disappointment on both sides in terms of the data, which came from an eight-month follow-up of the 128-patient study. Further analyses are ongoing, including a subcohort that received a repeat dose.

"It's disappointing there was not a stronger effect, but we should reserve judgement until the final data," Allsopp said.

Allsopp also reported progress in Pfizer's second cell therapy program, in which it is collaborating with researchers at University College London, who have generated retinal pigment epithelial cells from human embryonic stem cells. There is UK regulatory approval for a trial in age-related macular degeneration, and Allsopp said Pfizer has signed a manufacturing contract with Roslin Cells Ltd., of Edinburgh, Scotland.

"The product is being manufactured, and it will soon be in the first patients," Allsopp said.

Arnold Caplan, professor of biology at Case Western Reserve University and chief scientific officer at Orthocyte Corp., welcomed the fact that the Athersys/Pfizer cell therapy partnership is still in place and progressing.

"Our job as entrepreneurs is to engage other big pharma companies in the process of [development and commercialization] and pull them into a different way of thinking about our treatments," Caplan said. "Big pharma has to understand we have a cornucopia of molecules that are getting clinically significant results."

PRICING: BAR "GETS HIGHER EVERY TIME'

Such clinically significant data will be the key to getting reimbursement for cell therapy products at a time when health care budgets are shrinking around the world, said Michael May, CEO of Canada's Center for the Commercialisation of Regenerative Medicine (CCRM) in Toronto.

Under constrained budgets, the high price of cell therapies presents a huge barrier to market. "You have to displace existing technologies, and the bar gets higher every time," May said.

In the case of acute myocardial infarction, there are about 300 cell therapy trials in progress. But, May said, the standard of care currently means there is not much headroom.

According to a CCRM analysis, the most a payer would reimburse for an acute myocardial infarction treatment is $32,000, which is well below the current threshold for a cell therapy product.

However, in the case of sepsis, the lack of approved treatments and high mortality rates mean there is much more headroom and payers would be willing to pay $150,000.

"So you start to see perhaps that acute myocardial infarction is not where we should be investing," May said. While it may represent a large market, it will not be easy to get paid for a cell therapy treatment.

CCRM is now examining reimbursement issues at the earliest stages of selecting products to take into its manufacturing process development program.

Approaching reimbursement, as the next activity in the sequence following approval, certainly caused problems for Tigenix NV, the first company to have an autologous cell therapy product approved under the EMA's centralized route.

Chondrocelect, for treating knee cartilage injuries, gained approval in 2009, but to date it is only reimbursed in Belgium, the Netherlands and Spain.

"We didn't prepare ourselves in advance," said Maria Pascual, vice president of clinical operations and regulatory affairs at Leuven, Belgium-based Tigenix.

In April, the company threw in the towel and signed over marketing and distribution rights in return for royalties. Now Tigenix is making sure reimbursement is factored into the development of its other products. (See *BioWorld Today*, April 4, 2014.)

"You have to prepare for launch before you start phase III," Pascual told delegates. //

Chimerix

Continued from page 1

SEC, pricing 7.3 million shares at $14.22 each in a deal set to close next week.

Chimerix, of Durham, N.C., aims to use about $60 million from the public offering to help fund the recently begun phase III study with brincidofovir for the treatment of adenovirus infection, as well as another in kidney transplant patients and possibly more.

Brincidofovir began dosing in the SUPPRESS phase III trial last year for the prevention of cytomegalovirus (CMV) infection in hematopoietic cell transplant recipients. The compound is a broad-spectrum antiviral designed to block the replication of double-stranded DNA viruses, including CMV, and deploys in the conjugate cidofovir, a drug currently marketed as intravenous Vistide by Foster City, Calif.-based Gilead Sciences Inc. for treating CMV retinitis in AIDS patients.

For now, the standard of care in CMV is Valcyte (ganciclovir, Roche AG), which brings, like Vistide, toxic side effects and doesn't work to prevent the infection. Valcyte only comes into play after stem cell treatments have engrafted, which typically takes two to four weeks.

In March, the firm found itself spotlighted in the mainstream press and scorched in social media for its refusal to let dying 7-year-old Josh Hardy have brincidofovir on a compassionate-use basis. Chimerix solved its ethical conundrum with an open-label pilot study in immunocompromised patients with adenovirus infections, making the pivotal phase III study an extension of the pilot experiment. (See *BioWorld Today*, March 13, 2014.)

"The adenovirus trial pilot portion was initiated for the main part to provide access while we were finalizing the study design for the pivotal trial," explained CEO Michelle Berrey during the conference call with investors on first quarter earnings. "So that pilot portion does not have to have a certain number of patients. It's really to provide access while the study discussions are ongoing. We had initially discussed around 20 patients in the pilot portion. We are leaving that number open."

Chimerix ended the first quarter with almost $100 million in cash, which Piper Jaffray analyst Joshua Schimmer estimated would last "deep into 2015." With the new money, the firm stands in even better shape to push brincidofovir along. Plans for phase III trials for blocking CMV in solid organ transplants (primarily renal) and treating adenovirus infection are expected to be finalized with the FDA and European regulators by the end of this year. Enrollment in SUPPRESS should finish around the same time, with top-line results expected by mid-2015.

"The solid organ transplant study was our number two trial," Berrey said. "We were trying to get up and running in the first half of 2014, obviously, with the focus on adenovirus and the opportunity that we had to initiate that trial."

Though the start of the solid organ transplant experiment likely won't come until next year, "we are initiating our medical advisory group for a solid organ transplant study and have several opportunities to meet with that group over the summer to help lead us to what could be a successful study design that will be clinically relevant," Berrey said.

Cowen & Co. analyst Phil Nadeau is optimistic about brincidofovir launching in 2016, based on data from SUPPRESS. He pointed out in a research report that the phase II trial garnered a 73 percent reduction in CMV events. "However, there is reason to believe that the reduction will be even greater in phase III," Nadeau wrote. "In phase II, 50 of the 230 subjects with CMV reactivation had it prior to the first day of brincidofovir dosing. In phase III, brincidofovir can be dosed prior to engraftment, as early as day one, and therefore few patients should have reactivation prior to dosing."

Brincidofovir's net could stretch even wider. The compassionate-use program has provided "a wealth of information on its use to treat a wide range of viral infections, in a variety of patient populations," Nadeau wrote. This year, the firm will mine the database for new opportunities, which could include the John Cunningham (JC) virus, glioblastoma (apparently linked to CMV, according to some research, and where there have been recent publications establishing a link to CMV) and human papillomavirus-related papillomatosis. "Interestingly, brincidofovir has been used to treat eight patients with JC virus, and has cleared the virus from two," Nadeau wrote.

Morgan Stanley & Co. LLC and J.P. Morgan Securities LLC are acting as joint book-running managers for the offering, with Cowen and Co. LLC serving as co-lead manager. William Blair & Co. LLC and Canaccord Genuity Inc. are co-managing the deal. Chimerix has granted the underwriters a 30-day option to buy about 1 million more shares.

Shares of Chimerix (NASDAQ:CMRX) gained $1.98, or 13.9 percent, to close Wednesday at $16.20. //

OTHER NEWS TO NOTE

Glycomimetics Inc., of Gaithersburg, Md., said **Pfizer Inc.**, of New York, made a $15 million payment under the companies' 2011 collaboration to develop rivipansel (GMI-1070). Under the deal, Pfizer plans to initiate a phase III trial of rivipansel in vaso-occlusive crises in sickle cell patients, which will trigger an additional $20 million milestone payment to Glycomimetics upon dosing of the first patient in the trial. (See *BioWorld Today*, Oct. 12, 2011.)

Hemispherx Biopharma Inc., of Philadelphia, disclosed a preliminary-stage agreement required to manufacture Ampligen in Argentina in order to serve Latin American markets should Ampligen be approved in Argentina. The agreement is a prerequisite to the company starting the manufacture of stability lots, followed by stability testing, necessary to gain approval to manufacture Ampligen. In June 2010, Hemispherx inked a sales, marketing, distribution and supply agreement with **GP Pharm SA**, of Barcelona, Spain, for Latin America.

Voltarra

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lightning – a strategy underpinning the company's name – into phase III trials for its lead candidate. VOLT01 is a derivative of zoledronic acid (ZA), a bisphosphonate originally marketed by Novartis AG in a variety of indications, including osteoporosis, Paget's disease and bone cancers, under the trade names Reclast in the U.S., Aclasta in Australia and Zometa.

Bethlehem, Pa.-based Voltarra is collaborating with the Menzies Research Institute at the University of Tasmania in Hobart, Australia, on the multicenter trial, which is assessing the efficacy and safety of VOLT01 in knee osteoarthritis (KOA).

CEO Richard Becker, whose resume includes the oncology groups at Bayer Pharmaceuticals, Novartis and Merck & Co. Inc., formed Voltarra in September 2013 by acquiring the assets of IMC Biotechnology Inc., which was developing early stage spleen tyrosine kinase inhibitors and anti-tumor necrosis factor drugs, and Renascence Pharmaceuticals, which had a portfolio of late-stage product reformulations. The former CEOs of those companies, IMC's Renee Stewart and Renascence's Ketan Desai, are Voltarra's only other full-time employees, serving as chief scientific officer and chief medical officer, respectively.

Voltarra's early stage assets are on the back burner for now, while the company focuses on moving to market derivatives of compounds that advanced through phase II or beyond, demonstrated efficacy, but then stalled in the pipeline due to side effects or poor bioavailability.

VOLT01 is the first in line. ZA, administered intravenously, slows the loss of bone mass but is associated with a raft of post-dose side effects, including flushing, fever, joint pains and muscle aches. The VOLT01 formulation is designed to tamp down those side effects without sacrificing efficacy.

The market could be sizable. The Novartis drug had peak sales of $2.1 billion in 2011, falling back to less than $1 billion last year, according to Cortellis Competitive Intelligence.

Selection of KOA as the drug's initial indication involved a bit of serendipity. Several years ago, Menzies conducted a randomized, placebo-controlled study of ZA vs. placebo in patients with KOA, an off-label indication, with the trial partly funded by Novartis, Becker explained. Results, published in 2011, showed that a single 5-mg infusion of ZA in patients with KOA reduced pain and led to shrinkage of bone marrow lesions in the study, known as ZAP, which enrolled 59 patients.

However, the Menzies researchers wanted to follow a larger group for a longer time period. In June 2013, shortly before Voltarra was formed, the group launched a randomized, multicenter phase III study, known as ZAP2, comparing ZA to placebo. The ongoing trial, funded by grants and involving four sites in Australia, is designed to enroll 264 patients with KOA, with efficacy as the primary endpoint.

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Lysogene

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neurodegenerative disorder arising from impaired breakdown of the cell surface and extracellular matrix component heparan sulfate.

Also called mucopolysaccharidosis III, it is the most prevalent and severe of four related lysosomal storage disorders that have devastating effects on patients' intellectual and motor development and that lead to an early death.

So far, just four Sanfilippo type A patients have received the therapy in an open-label phase I/II trial. "The next step for us is to prepare for pivotal studies," Karen Aiach, CEO and co-founder of Lysogene, told *BioWorld Today*. The company aims to begin the pivotal program by the end of 2015. In rare diseases, this kind of trajectory is not uncommon. "We even know of some groups who are aiming to enter directly into phase I/II/III studies in rare diseases with innovative therapies," she said.

The Paris-based firm also plans to commence development of a second gene therapy treatment in an undisclosed indication. It aims to file a clinical trial application by the end of 2016.

SAF-301 comprises an adeno-associated viral (AAV) vector serotype 10 carrying two genes, SGSH and SUMF1, which encode N-sulfoglucosamine sulfohydrolase and sulfatase-modifying factor 1, respectively. The former is part of the heparan sulfate breakdown pathway and is absent in patients with Sanfilippo syndrome type A.

In the SAF-301 trial, the construct was injected directly into the patients' brains via a stereotactic procedure. Each received a dose of 7.2 x 1011 viral genomes, delivered over a two-hour period from a 12-needle device. "It's mainly a neurological disease, with very mild peripheral symptoms," Aiach said. The limited scale of the study means that whatever conclusions can be drawn must necessarily be tentative. "The primary endpoint was safety," she said. "The second objective of the study was to explore potential future efficacy endpoints." The construct appeared safe and well tolerated and, despite being on immunosuppressive therapy, the patients did not exhibit an increase in infection.

SUMF1 plays a role in the post-translational modification and catalytic activation of sulfatase enzymes. The company plans to dispense with that aspect of the therapy in the upcoming pivotal study – it is present in patients in any case.

A report of the trial, titled "Intracerebral Administration of Adeno-Associated Viral Vector Serotype rh.10 Carrying Human SGSH and SUMF1 cDNAs in Children with Mucopolysaccharidosis Type IIIA Disease: Results of a Phase I/II Trial," was published online on May 5, 2014, in *Human Gene Therapy*. Three of the four patients treated were between 5.5 and 6 years of age, at which point the condition is relatively advanced. All were able to walk, but they had abnormal cognitive abilities and exhibited brain atrophy. The fourth was 2 years and 8 months and, according to the study authors, "was the most likely to display neurocognitive benefit." Modest improvements in behavior, attention and sleep were evident in the other three patients. Brain atrophy, measured by nuclear magnetic resonance imaging, appeared stable in two patients but increased in two others, including the youngest patient. A follow-up observation trial is ongoing.

Meanwhile, Lysogene will embark on a slew of activities in advance of the pivotal studies, including embarking on a manufacturing campaign, engaging with drug regulators and patient groups, and selecting and preparing clinical trial sites. It plans to seek a pre-investigational new drug application meeting with the FDA with a view to including U.S. sites in the development program. Manufacturing will be carried out at the UCL Partners Gene Therapy Consortium at University College London. Aiach's co-founder, Olivier Danos, previously was director of that unit and established the AAV facility there.

The funding round was led by Paris-based Sofinnova Partners, which was also the company's seed investor. Other participants in the new investment include Bpifrance, through its Innobio fund, and Novo Seeds, the early stage investment arm of Novo A/S.

Sofinnova Partners was attracted to the company on the basis of the therapeutic potential of its lead program, not its technological profile as a gene therapy. "For this disease, we think this is the best approach," Rafaèle Tordjman, managing partner at Sofinnova, told *BioWorld Today*. "It's not more high-risk than usual. Obviously gene therapy is challenging," she said. But the technical challenge is offset by the more limited clinical development requirements. The eventual European approval of Uniqure BV's Glybera (alipogene tiparvovec) to treat familial lipoprotein lipase deficiency is further encouragement, notwithstanding the tortuous approval process the dossier went through. "It's probably not the easiest or best case, because it's not a lethal disease," Tordjman said.

There is no approved therapy for any of the Sanfilippo syndromes as yet. Dublin-based Shire plc has completed a phase I/II trial of an enzyme replacement therapy for type A, SHP610, which it plans to move into a phase IIb trial. Uniqure, of Amsterdam, the Netherlands, is collaborating with the Pasteur Institute in Paris on a gene therapy approach for Sanfilippo syndrome type B. A phase I/II trial is ongoing. //

OTHER NEWS TO NOTE

Imaginab Inc., of Los Angeles, said it formally launched Imaginab Japan KK, a wholly owned subsidiary based in Tokyo, aimed at better meeting the commercial needs of several significantly clinical development and partnering opportunities, the company said. The subsidiary will be led by Shintaro Nishimura.

Regulatory front

Continued from page 1

drugs and devices.

Unanimously passed by the Louisiana Legislature, the bill was sent to Gov. Bobby Jindal Tuesday for his signature. HB 891 mirrors the legislation Colorado Gov. John Hickenlooper signed into law Saturday. Other states are following suit. The Missouri General Assembly is working on a similar bill, and "right-to-try" will be on the November ballot in Arizona.

The state legislation does nothing to extend compassionate use beyond what the FDA already permits, but it shows there is a problem with getting access to promising therapies, Rep. Harold Rogers (R-Ky.) said at Tuesday's House subcommittee hearing on ways to speed the development of new cures. (See *BioWorld Today*, May 21, 2014.)

Citing the lengthy approval process of investigational drugs and devices, the Colorado and Louisiana legislation noted that patients with terminal illnesses don't have the luxury of waiting until a drug or device receives FDA approval.

Although the legislation recognizes a right to try, it does not force manufacturers to provide investigational drugs or devices. It also doesn't require third-party payers to cover the unapproved therapies. And it shields health care providers and drug- and devicemakers from liability associated with the compassionate use of an investigational product.

When the experts testifying at the subcommittee hearing were asked about the right-to-try bills, Garry Neil, head of global R&D at Medgenics Inc., said the cost of providing an investigational therapy for compassionate use can be prohibitive for small companies.

Sara Radcliffe, executive vice president of the health section at the Biotechnology Industry Organization, added that compassionate use is a difficult, complex issue. The written testimony she submitted detailed the growing delays in development that are making compassionate use a front-burner issue with patients.

For instance, the duration of the clinical phase of drug approvals has steadily lengthened from an average of 4.6 years in 1990-1994 to an average of 7.1 years in 2005-2009. That increase has been accompanied by rising protocol complexities and declining enrollment and retention rates.

"Confronting the problem of increasing costs and durations of clinical trials is a daunting task," Radcliffe said in her testimony.

While industry is committed to partnering with Congress, the FDA, NIH, patients, academia and other stakeholders to improve the efficiency of clinical trials to reduce the barriers to new therapies, patients who are out of options don't have time to wait for those talks to produce results. Many of them have turned to social media to pressure drug- and devicemakers to grant them compassionate use.

Chimerix Inc., of Durham, N.C., was recently the target of a social media firestorm to get it to provide its antiviral candidate brincidofovir to a dying 7-year-old boy, whose immune system had been compromised following a round of cancer treatments. The issue for Chimerix was the cost involved, which could delay its ongoing development program and, thus, the approval and marketing of the drug for other patients. (See *BioWorld Today*, March 13, 2014.)

South Plainfield, N.J.-based PTC Therapeutics Inc. ended up in court when a patient sued for access to its investigational drug. While PTC won in district court, it lost on appeal. Rather than draining limited resources in court battles and compassionate use programs, "the right thing is to get the drug approved and commercially available as rapidly as possible," PTC CEO Stuart Peltz told *BioWorld Today*. That way the new treatment is available to all patients, not just a select few.

One solution would be for the U.S. to adopt something like the EU's conditional approval program, which grants access to some investigational therapies once clinical trials are completed, Peltz said. However, PTC was denied conditional approval in the EU of its ataluren, a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation. The company is appealing. (See *BioWorld Today*, May 14, 2014.)

PTC's 48-week, 220-patient confirmatory phase III trial for ataluren is on track to complete enrollment in a few months, with top-line data expected in mid-2015. The process of developing ataluren from the idea stage has taken 15 to 16 years, Peltz said. During that time, the biotech has had to raise money, develop the clinical path for the novel drug and educate regulators about the disease and the science behind the drug.

CMS FINALIZES RULE

After withdrawing the most controversial parts of a proposed rule revising the Medicare Part D prescription drug program, the Centers for Medicare & Medicaid Services (CMS) has finalized the rule.

The final rule, which is to be published in Friday's *Federal Register*, gives CMS enhanced tools to fight fraud and abuse in the prescription drug program. To ensure that Part D drugs are only prescribed by qualified individuals, the rule requires prescribers to enroll in Medicare by June 1, 2015. It also gives CMS the authority to revoke a physician's Medicare enrollment for abusive prescribing practices and patterns.

Another provision will broaden public access to privacy-protected Part D data, such as unencrypted, prescriber, plan and pharmacy identifiers contained in prescription drug event records.

The nearly 700-page proposed rule CMS released for comment in January also would have reduced the number of Part D plans a sponsor could offer, set standards on requirements to participate in preferred pharmacy networks, clarified noninterference provisions and lifted the protected class designation for antidepressants, immunosuppressants and, in the future, antipsychotics.

The agency backed away from those provisions after it was

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Insulin

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inhibitor that they used to probe IDE's role more specifically than knockout mice could.

In their studies, they showed that in both lean and obese mice, IDE regulated not just insulin, but also glucagon and amylin, two hormones that control blood sugar levels. When mice were fed glucose, acute treatment with IDE improved their blood sugar levels.

"These findings demonstrate the feasibility of modulating IDE activity as a new therapeutic strategy to treat type 2 diabetes and expand our understanding of the roles of IDE in glucose and hormone regulation," the authors concluded. Their work appeared in the May 22, 2014, issue of *Nature*.

Editor's note: This is an outtake from BioWorld's Bench Press, a weekly addition to the daily news in which BioWorld takes a look at translational medicine. For more science news like this, look for the attachment every Monday morning, or visit BioWorld's dedicated science portal, The BioWorld Biome: Our Habitat for All Things Science at www.bioworld.com.

Regulatory front

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swamped with more than 7,500 comments and Congress threatened to pass a bill preventing it from implementing any Part D provision included in the rule. (See *BioWorld Today*, March 4, 2014, and March 12, 2014.)

'SAMENESS' TOOL NEEDED

The FDA will accept applications next month for a multiyear grant of up to $1 million to develop a mathematical algorithm or model to use in determining similarity or sameness of biosimilars and generic versions of complex drugs.

In providing a "coherent picture" of the molecular structure of complex macromolecules or drug substances, the project to be funded by the grant could help determine the extent of preclinical and clinical studies that will be needed to develop copies of the drugs.

Initially, "the model will be used to qualitatively and quantitatively determine the degree of sufficiency of in vitro chemical and biological characterization assays, with respect to demonstrating similarity (or sameness) among multiple batches of the reference product," the FDA said.

Details about the project and grant are available on the NIH's grants webpage. //

OTHER NEWS TO NOTE

Inhibikase Therapeutics Inc., of Atlanta, said it received FDA orphan drug designation for imatinib to treat progressive multifocal leukoencephalopathy (PML), a rare side effect of small-molecule and antibody drugs given to patients with autoimmune diseases such as arthritis and multiple sclerosis and a disease that occurs in 1 percent to 3 percent of clinical AIDS patients. Imatinib, the active ingredient in the firm's lead drug, IkT-001Pro, (and also the active ingredient in Novartis AG's Gleevec), is a host-directed protein kinase inhibitor that disrupts the ability of JC virus, which is activated in cases of PML.

Lanthio Pharma BV, of Groningen, the Netherlands, said it was awarded an Innovation Credit loan of up to €3.6 million (US$4.9 million) by Dutch government agency RVO. The loan is risk bearing and will be matched by Lanthio's investors and is expected to cover up to 35 percent of development costs through to completion of phase II trials. It will support the development of LP2, a lanthiopeptide designed to selectively activate the angiotensin type 2 receptor of the renin angiotensin system, for treatment of idiopathic pulmonary fibrosis.

Cour

Continued from page 1

veteran Catherine Mackey as chairman of its board.

Founded in 2012, the Elmhurst, Ill.-based Northwestern University spinout is still preclinical. But it already has two yet-to-be-named big pharma collaborators in place and anticipates adding a third by the end of the year, Cour CEO and president, John Puisis, told *BioWorld Today*.

Cour's immune-modifying nanoparticles (IMPs), based on work done at the University of Sydney and Northwestern University, are derived from biodegradable polymer polylactic-co-glycolic-acid (PLGA) and have the potential to address a variety of inflammatory conditions.

The negatively charged particles bind to the positively charged MARCO receptor of monocytes, directing them to the spleen for destruction through apoptosis, thus diminishing inflammation. Inflammatory monocytes are prevented from entering sites of injury or inflammation, reducing tissue damage and accelerating repair and recovery.

The company's tolerizing immune-modifying nanoparticles (TIMPs) also employ PLGA nanoparticles, but load them with antigen-specific proteins that induce immune tolerance. In the case of specially programmed TIMPs, the modified particles can be used to deliver toleragenic signals to antigen-presenting cells, resulting in long-term immune tolerance.

At the heart of the technology are proprietary modifications to the nanoparticles that determine the immune target and mechanism of action, while the particle itself biodegrades and is then cleared by the body.

So far, Cour has filed patents to encapsulate hundreds of epitopes that modulate cell response. The highly specific TIMPs are at the core of its pharma partnerships in type 1 diabetes, celiac disease and a third yet-to-be-named autoimmune disorder. It's diabetes partner has an exclusive option on its investigational TIMP, while its celiac partner has an exclusive evaluation option.

Supported by the stable foundation of its partnerships, Cour plans to advance its internal IMPs in several cardiovascular indications, including acute myocardial infarction, acute encephalitis syndrome and, once lead optimization is complete, ischemic stroke and inflammatory bowel disease.

So far, Puisis said, the company has raised enough seed capital to fund its needs. "Our goal is to see how these collaborations play out and determine our capital needs going forward," he said. As the company further explores applications for its platform and tackles the strategic thinking necessary to build a stable foundation, it was just the right time to bring Mackey on board, he said.

Mackey, an experienced corporate director, brings 30 years of operating experience in the biopharma and agricultural industries. She served as senior vice president of worldwide R&D and site director for La Jolla Laboratories between 2001 and 2009 and has advised a number of other start-ups.

"When I looked at Cour and compared it to other start-ups, they have an enormous amount of data, an impressive patent portfolio, and have only taken nondilutive funding," Mackey noted. "They've built a very solid foundation. As a platform, it's not a one-trick pony."

Indeed, Cour, which gained its name after company co-founders voted over dinner to incorporate the ideas of courage and heart, may have many tricks ahead. "There are many discoveries yet to be made," Puisis said. "We're still identifying immune pathways we want to explore further, and there are lot of opportunities left to be realized there." //

OTHER NEWS TO NOTE

Neurotez Inc., of Ridgewater, N.J., said it executed an exclusive license deal covering its Leptin derivatives for the treatment of Alzheimer's disease and other cognitive disorders with **GCA Therapeutics Ltd.**, of New York. Under the terms, GCA gets rights to clinically develop and commercialize Leptin products in mainland China, exclusive of Hong Kong, and Taiwan, and will assume all development and regulatory responsibility. In exchange, Neurotez will be eligible for gross sales milestones of up to $102.5 million, plus royalties on gross sales. The license also has certain minimum annual sales thresholds following first commercial sales in mainland China.

Nuvilex Inc., of Silver Spring, Md., said it, along with the Translational Drug Development (TD2) in Scottsdale, Ariz., started preparing for a U.S.-based preclinical and clinical studies on the pain and accumulation of fluid in the abdominal cavity, two commonly occurring symptoms associated with advanced pancreatic cancer. TD2 will study the effectiveness of Nuvilex's pancreatic cancer treatment in relieving the pain and fluid accumulation known as ascites. The treatment combines the Cell-in-the-Box live-cell encapsulation technology with cancer agent ifosfamide and will be studied to see if it can improve the quality of life of pancreatic cancer patients. Preclinical studies are set to commence shortly.

Supernus Pharmaceuticals Inc., of Rockville, Md., said **United Therapeutics Corp.**, of Silver Spring, Md., paid the firm a $2 million milestone upon United's launch of Orenitram (treprostinil) extended-release tablets for the treatment of pulmonary arterial hypertension in the U.S. Orenitram uses a Supernus technology platform. In addition to the launch milestone, Supernus is eligible for royalties on net sales and may be entitled to additional milestones. Orenitram gained approval late last year. (See *BioWorld Today*, Dec. 24, 2013.)

Voltarra

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'PARTNERING CERTAINLY WOULD BE PREFERRED'

As Voltarra came together, Desai contacted the Menzies team to discuss comparative data on VOLT01 and the Novartis drug to determine whether the company's findings were consistent with results they had seen in ZAP. Not only were the data in line, but the Menzies researchers approached the four sponsoring institutions and the country's regulatory agency, the Therapeutic Goods Administration, seeking to add a third arm to the trial, Becker said.

The proposal was accepted, and VOLT01 was added to the two-year randomized, multicenter, placebo-controlled, double-blind trial, conducted under the auspices of Medicines Australia.

"The hopes are, whoever wins – and I'm assuming it's not going to be placebo – the compound would be moved forward to the Therapeutic Goods Administration for potential registration" in KOA, likely in 2015, Becker told *BioWorld Today*.

In the meantime, the trial includes a pre-planned six-month interim analysis after the study is fully enrolled, which Becker estimated will occur in the first quarter of 2015. At that point, "we are going to know how VOLT01 has performed vs. Aclasta" in terms of safety and efficacy, he said. Though long-term monitoring will continue in the study, Voltarra plans to package the early data and request face-to-face meetings with the FDA and the EMA to seek guidance on the design of a global registration study.

Provided the company can conduct those meetings by mid-2015, Becker predicted the phase III registration program could be completed by 2017, with subsequent regulatory filings steering the product toward approval in 2018.

In the U.S., Voltarra expects to file its new drug application for VOLT01 under the 505(b)(2) pathway, "which saves a boatload of money, since we don't have to go back and reinvent the wheel," Becker said, noting that the drug's preclinical, phase I and tox studies are complete. The company hopes to file concurrently with the EMA, using essentially the same data package. The company has filed provisional and non-provisional patents and expects to hold a broad patent estate for VOLT01 to prevent and treat osteoarthritis.

To fund its ambitious program, Voltarra has a complex curcumin, dubbed VOLT03, that is sitting "in the parking lot" while other companies conduct proof-of-concept studies with similar compounds across applications in oncology, inflammatory indications and neurodegenerative diseases. Approximately 80 trials with curcumin alone or in combination with other interventions are under way, according to Cortellis Clinical Trials Intelligence, with most in phase II or III.

"We're just sitting back to see if one of those trials is positive," Becker admitted. "Then, potentially, we can move into that space with our product, which is also reformulated to make the curcumin more soluble."

VOLT03 will move to market as a neutraceutical, with quick sales – albeit more modest than a prescription drug – creating a revenue stream to help offset the remainder of the VOLT01 clinical development program.

Voltarra also is in the middle of a pre-seed round that will likely stay south of $1 million, Becker said, with plans for a larger series A on tap for later in the year. Once regulatory filings for VOLT01 are under way, the company will decide whether to seek a series B.

"Partnering certainly would be preferred," Becker said. "I'm going to need a partner to help from the marketing and sales end anyway. If I can find one to help with the clinical end, as well, that would be ideal, but I'm not counting on that." //

OTHER NEWS TO NOTE

Wilex AG, of Munich, Germany, said a collaboration agreement with **UCB SA**, of Brussels, Belgium, for product candidates WX-554 and WX-037 and three preclinical antibody programs was terminated by mutual agreement due to an extensive restructuring at Wilex, which the company disclosed in January. The strategic alliance, inked early in 2009, was worth €10 million up front (US$13.5 million) and a potential €10 million in two near-term milestones to Wilex, which will return to UCB all rights and transfer all intellectual property, data and documents generated in connection with the programs. An agreement regarding an antibody program for non-oncology indications that was signed last year was terminated. Wilex will receive a final payment from UCB for R&D expenses, and UCB agreed to waive repayment of the €2.5 million shareholder loan granted in December 2010 on completion of the transfer. Termination of the agreement does not affect UCB's role as a Wilex shareholder. (See *BioWorld Today*, Jan. 12, 2009.)

IN THE CLINIC

Amgen, of Thousand Oaks, Calif., said *The New England Journal of Medicine* published results from a phase I study suggesting that inhibiting thymic stromal lymphopoietin (TSLP) could benefit the treatment of asthma. TSLP is a cytokine thought to be a key driver of allergic inflammation. Results from the 31-patient proof-of-concept study showed treatment for 12 weeks with AMG 157, a monoclonal antibody that inhibits the activity of TSLP, resulted in statistically significant reductions in early asthmatic responses and late asthmatic responses in the airways following allergen challenges in patients with allergic asthma. The data also showed statistically significant decreases in baseline markers of inflammation in the airways. Overall, adverse events were similar across treatment and placebo groups, with no serious adverse events. The compound, in joint development with **Astrazeneca plc**, of London, through its biologics arm Medimmune, is in phase II development in asthma. The phase I findings also were presented at the American Thoracic Society international conference in San Diego.

IN THE CLINIC

Antibe Therapeutics Inc., of Toronto, said it submitted a clinical trial application to Health Canada for lead drug ATB-346, proposing a phase I study to assess the safety, tolerability and pharmacokinetics of single and multiple-ascending doses in healthy subjects. The trial is slated to start this summer. ATB-346 is a hydrogen sulfide-releasing derivative of naproxen.

Atyr Pharma Inc., of San Diego, said it completed a phase I study for its lead program, Resokine IV, which marked the first ever administration of a physiocrine to humans. The double-blinded, placebo-controlled trial was conducted in healthy male and female subjects in the European Union to assess the safety and tolerability of Resokine IV, in development as a potential therapeutic for rare immune disorders. The company said the data from 32 healthy subjects in four dose cohorts support the basic premise of Resokine IV as an immunomodulator rather than a classic interleukin or interferon with systemic immunostimulating properties upon administration. Among their various homeostatic functions, some physiocrines act as extracellular signaling molecules to orchestrate immunohomeostasis in response to stress and other physiological changes. Physiocrines comprise naturally occurring proteins derived from tRNA synthetases that play fundamental roles in the function of human physiology and restoring pathophysiological states to a healthier state.

Celsion Corp., of Lawrenceville, N.J., said the FDA has green-lighted its planned pivotal phase III trial of Thermodox, its heat-activated liposomal encapsulation of doxorubicin, in combination with radio frequency ablation (RFA) in primary liver cancer, or hepatocellular carcinoma. The trial will enroll 550 patients globally and evaluate Thermodox in combination with RFA vs. standardized RFA alone. The primary endpoint for the trial is overall survival. An independent data monitoring committee will conduct two interim analyses. Celsion said it expects to launch the study before the end of June.

Gilead Sciences Inc., of Foster City, Calif., reported results from a placebo-controlled, phase IIa challenge study of GS-5806, an investigational oral RSV fusion inhibitor, in healthy adult patients intranasally infected with respiratory syncytial virus (RSV). The trial achieved its primary and secondary endpoints of lower viral load (the amount of virus detected in the nasal wash), improvements in total mucus weight (the amount of mucus produced by the nose) and also symptom diary score compared to placebo. The results are being presented during a poster discussion session at the American Thoracic Society conference in San Diego.

Intelgenx Corp., of Saint Laurent, Quebec, and **Redhill Biopharma Ltd.**, of Tel Aviv, Israel, reported data from a comparative bioavailability study with migraine candidate Versafilm, an oral thin film formulation of rizatriptan for acute migraines. Results of the study are subject to final quality assurance and an independent study report by the Canadian clinical research organization that conducted the trial, but the companies said the data will support the planned submission in Europe for the product during the third quarter.

Nymox Pharmaceutical Corp., of Hasbrouck Heights, N.J., reported results from the Brief Male Sexual Function Questionnaire in its recently completed NX03-0040 study of NX-1207 in low-grade localized prostate cancer, indicating that targeted treatment with the drug at either dose – 2.5 mg or 15 mg – had no significant effect on reported sexual function score post-treatment. Nymox also is testing NX-1027 in benign prostatic hyperplasia and recently completed the second pivotal trial in that indication.

Summit plc, of Oxford, UK, said SMT C1100, an oral small-molecule utrophin modulator for the treatment of Duchenne muscular dystrophy (DMD), successfully met its primary endpoint of safety and tolerability in a phase Ib trial in patients with the disease. The dose-escalating trial was conducted in 12 patients with DMD, between 5 and 11 years old. The nonplacebo-controlled study also measured levels of creatine kinase (CK), an enzyme associated with muscle fiber damage that is elevated in boys with DMD, and results found that In the majority of patients there was a reduction in CK levels during dosing with SMT C1100. Those data are consistent with nonclinical in vivo efficacy studies in the mdx model of DMD that showed SMT C1100 reduced CK levels after only 15 days. The company plans to review those preliminary data, which are expected to lead to a revision of future clinical trial plans in order to determine the optimal way, either through dietary means or drug formulation changes, to address the drug uptake differences between DMD patients and healthy volunteers. The next patient study is now expected to start in the fourth quarter.

PHARMA: OTHER NEWS TO NOTE

Abbvie Inc., of Chicago, said the FDA granted Humira (adalimumab) orphan drug designation for the treatment of non-infectious intermediate, posterior or pan-uveitis, or chronic non-infectious anterior uveitis, a group of rare but serious inflammatory diseases of the eye. Abbvie is investigating the efficacy and safety of Humira for the treatment of non-infectious uveitis, and the clinical program is in phase III development.

Baxter International Inc., of Deerfield, Ill., said the FDA extended the PDUFA date for its review of the biologics license application for Hyqvia (immune globulin infusion 10 percent [human] with recombinant human hyaluronidase), the company's investigational subcutaneous treatment for patients with primary immunodeficiency. The FDA is requiring additional time to review supplemental data that Baxter provided as part of the ongoing process for approval. The PDUFA date has been extended by three months, which is the standard extension period. As part of the FDA's extended review, Baxter now expects to participate in a Blood Products Advisory Committee meeting, which the agency has scheduled for July 31. Hyqvia was approved by the European Commission in 2013 and is available in several European countries, including Germany, the Netherlands, Sweden, Norway, Denmark, Ireland and Italy.

Daiichi Sankyo Co. Ltd., of Tokyo, began a three-year research project with Sanford-Burnham Medical Research Institute, of La Jolla, Calif., to investigate cardiovascular-metabolic diseases. Terms of the agreement, which will deploy Sanford's screening capabilities, were not disclosed.

Novo Nordisk A/S, of Bagsvaerd, Denmark, said the FDA tentatively scheduled an advisory committee meeting for Sept. 11 to discuss the new drug application (NDA) for liraglutide 3 mg for the treatment of obesity. The NDA was submitted to the FDA last December.

PHARMA: IN THE CLINIC

Boehringer Ingelheim GmbH, of Boehringer, Germany, presented results from the phase III VIVACITO study at the American Thoracic Society meeting in San Diego, showing that the fixed-dose combination of tiotropium and olodaterol, delivered via the Respimat inhaler, demonstrated a statistically significant improvement over both monotherapy treatment ($p < 0.0001$) and placebo ($p < 0.0001$) in the primary endpoint, defined as the forced expiratory volume in one second. Secondary endpoints included additional tests measuring breathing over 24 hours. The overall incidence of adverse events was comparable among treatment groups.

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