New study reveals why the gastrointestinal microbiota affects disease

BY ZACK ANCHORS

GOTHENBURG, Sweden—Several studies in recent years have found evidence that the unique mix of bacteria in an individual’s gut is associated with their vulnerability to various health disorders. Until now, however, scientists had not pinpointed the particular mechanisms through which different kinds of gut bacteria affect health.

A new study published in Molecular Systems Biology has shed light on how it works. Research conducted at Chalmers University of Technology, the Royal Institute of Technology, and the University of Gothenburg in Sweden found that gut bacteria regulate a key antioxidant found in every human cell. Deficiencies of that antioxidant, glutathione, contribute to oxidative stress, which plays an important role in several lifestyle diseases.

The goal of the study, first author Adil Mardinoglu tells DDNews, was to investigate “the global metabolic differences between two mice that could be directly linked to the presence of the bacteria in mice.” Mardinoglu, an assistant professor at Chalmers, and other researchers accomplished this by creating a generic map of mouse metabolism and tissue-specific computer models for major mouse tissues. They found that the microbiota in the small intestine consumed glycine, which is one of the three amino acids required for the synthesis of glutathione.

FDA beats the averages on approvals

FDA’S CENTER FOR DRUG EVALUATION AND RESEARCH APPROVES 45 NOVEL NEW THERAPIES IN 2015

BY JEFFREY BOULEY

SILVER SPRING, Md.—The new year brought many gifts for patients and clinicians in the form of 45 novel new therapies approved by the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA), significantly more than the average of 28 the agency has approved during the previous nine years of the past decade.

“But far more important than quantity—and the valuable new roles many of these drugs can serve in advancing medical treatments for patients with multiple myeloma. The organizations presented these findings in a poster session at the American Society of Hematology (ASH) Annual Meeting.

Potential drivers of clinical outcomes and their associated molecular pathways, including some that may be novel, have begun to emerge from the largest and most comprehensive computer models of molecular and clinical interactions in multiple myeloma. These drivers and molecular pathways may represent targets for drug discovery and development, leading to new pharmaceutical strategies that prevent progression of disease and address continued unmet treatment needs of multiple myeloma patients.

The computer models are the product of large-scale, multimodal patient data from the MMRF’s landmark CoMMpass Study and the revolutionary GNS Bayesian causal inference learning and simulation platform REFS (Reverse Engineering Molecular Systems Biology).
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Pharma outsourcing M&As marked record year in 2015

LONDON—A drastic increase in merger and acquisition (M&A) activity propelled the value of pharmaceutical outsourcing deals from $9.9 billion in 2014 to nearly $8.4 billion in 2015, putting the sector on track for a record-breaking year, according to an analyst with research and consulting firm GlobalData.

In an article for Arena International’s Clinical Trial Year Book 2016, Adam Dion, GlobalData’s senior healthcare industry analyst, says that while the pharmaceutical outsourcing services sector has seen a sharp rise in M&A activity in recent years, the value of deals has more than doubled over the past year, from $5.5 billion in 2014, to $12 billion by October 2015.

“This year has seen a number of high-valued transactions, including LabCorp’s $6.1-billion purchase of Covance, and WuXi being sold for $3.3 billion to a Chinese private equity group,” Dion explained, adding: “Contract manufacturers have also been busy in 2015. Sigfried Holding AG, an API maker based in Switzerland, bought BASF’s pharmaceutical outsourcing services. Pfizer bought Kremers Urban Pharmaceutical supply business, and Lannett acquired Kremers Urban Pharmaceutical supply business, and Lannett acquired Kremers Urban Pharmaceuticals, a specialty generic drug maker and subsidiary of UCB, for $1.2 billion.”

“The CRO sector has enjoyed impressive growth over the past few years, as plummeting sales from the loss of exclusivity branded drugs, the high cost of pharmaceutical research and development and the globalization of clinical trials, have led to a surge in demand for outsourced clinical trial work. “GlobalData expects that Covance will act as a separate entity under the LabCorp moniker, in which LabCorp can leverage Covance’s leadership in clinical trials monitoring, patient and sponsor recruitment and study site selection through its proprietary Xcellerate technology platform.”

Can pharma companies survive in a digital world?

GLOBAL RESEARCH and consulting firm Frost & Sullivan notes that with digital health investments reaching $8.4 billion in 2015, “the digital uprising is transforming the healthcare industry,” and “as the digital world is expanding, many are questioning how pharmaceutical companies will stay ahead of these changes.”

According to Frost & Sullivan Senior Vice President Greg Caressi, who works in the organization’s Transformational Health group, filling the prescription for this shift will pose a “huge challenge” for Big Pharma.

Pharmaceutical companies seem to have three options, he relates, the first being to “embrace the risks and challenges, which is not part of the corporate culture for most pharmaceutical organizations.” Second is to collaborate, which he notes we have seen more and more of over the years. Third is to reinvent companies and adopt new business models, but he noted, that “this is frowned upon until prices for branded drugs fall farther and faster.”

“Eventually, most pharmaceutical organizations will be able to steer the huge ship towards only one of these three shifts,” Caressi maintains. “There are few incentives for major risks while investors require big numbers from the existing model, and most digital initiatives are marginal efforts at best, not big plays that are expected to drive even 10 percent of revenues.”
NEW YORK—As it does on a regular basis, GBI Research has pulled out its crystal ball to predict the track of several areas of treatment of interest to pharma and biotech, and finds growth, albeit all of them, through with varying success and some caveats.

**Immunology**

Dominic Trewartha, a managing analyst for GBI, says the global immunology treatment market “is a lucrative area, as up to 7 percent of Western populations are thought to be affected by chronic immunological disorders.” Consequently, the element of cost for immunology is considerable, with 1,826 products currently in active development, though he adds that “While 85 of these are in Phase 3, the process must be acknowledged that 73 percent of these pipeline products are in early developmental stages.”

Looking at the specific numbers, GBI predicts the market is set to expand from $61.5 billion in 2015 to reach $74.2 billion in 2022, adding that the immunology treatment market’s compound annual growth rate (CAGR) will equal a relatively stable 2.71 percent due to practical and regulatory barriers to entry for biosimilars that are not present for small-molecule generics, and thanks to a moderately strong late-stage pipeline.

GBI Research’s study suggests there are a number of prospective products expected to achieve strong annual revenues during the forecast period, although these are not anticipated to achieve revenues comparable to those generated by the current strongest-selling immunology products.

Trewartha explains: “To date, the most clinically and commercially effective drugs have been in a class of compounds known as monoclonal antibodies (mAbs), which includes blockbuster products such as Humira (adalimumab) and Remicade (infliximab). APB-501, a biosimilar of Humira, which was the best-selling drug of 2014 worldwide, is anticipated to generate annual revenues of almost $1 billion by 2022, making it an exceptionally strong-performing non-patented drug.”

The analyst adds that while the immunology therapeutics market is a very commercially active area, with a number of exceptionally high-selling products present, revenues for these key drugs are expected to undergo a steady decline towards the end of the period. Trewartha concludes: “GBI Research believes that revenues for immunology therapeutics will only significantly decline in the long term, beyond the forecast period. This is due to the protective effect of the practical and regulatory challenges in fielding biosimilar products, which reduces the impact of patent expiries on biologics, compared with small molecules.”

**COPD**

The global treatment market for chronic obstructive pulmonary disease (COPD), for its part, will rise steadily at a CAGR of 2.9 percent from $9.2 billion in 2014 to $11.2 billion in 2021, the business intelligence organization asserts.

Yasser Mustaq, a senior analyst for GBI, states that the relatively unchanging incidence rate of COPD is largely due to the decline of tobacco smoking in many developed nations, combined with the fact that an ever-aging population will be more susceptible to the disease.

“The COPD therapeutics market landscape over the forecast period will be characterized by the sales erosion of leading brands,” Mustaq maintains. “Currently, the market is dominated by three brands, namely Pfizer’s Spiriva, GlaxoSmithKline’s (GSK’s) Advair and AstraZeneca’s Symbicort, which have all generated multibillion-dollar revenues to date. The patents for these leading brands have either expired or will do so very soon, leaving the market open to generic competition, which will impact negatively on these brands’ sales figures.”

GBI Research also notes that despite the patent expirations for key therapies, the market will see the approval of multiple high-profile products from 2015. However, the majority of these will represent addition-in-class products, which will likely only offer incremental improvements over existing ones.

“The market, which used to be dominated by only a few brands, will become more fragmented and will see the introduction of various brands with similar characteristics,” according to Mustaq. “Currently, none of the available therapies have been shown to modify long-term disease progression, leaving a strong need for a disease-modifying therapy that targets the natural history of the disease. This presents an attractive opportunity for major pharma players.”

**Diabetes**

Meanwhile, the type 1 diabetes mellitus (T1DM) market across the eight major countries of the United States, Canada, France, Germany, Italy, Spain, the United Kingdom and Japan will expand from $4.3 billion in 2014 to $7.1 billion by 2021, at a more robust CAGR of 27 percent, according to GBI. This rise will be driven by the uptake of recently approved and pipeline premium products, as well as the rapidly expanding treatment population, which is attributable to the increasing incidence of T1DM, as well as the fact that patients are being diagnosed at younger ages and living longer due to improved treatment options.

Fiona Chisholm, an analyst for GBI, says that while the T1DM market faces the threat of considerable biosimilar erosion over the forecast period, owing to recent and upcoming patent expirations for several of the leading insulin brands, such as Sanofi’s Lantus, Eli Lilly’s Humalog and Novo Nordisk’s Levemir and Novolog, there are reasons to be optimistic.

“Despite this apparent market vulnerability, all of these companies have strong pipeline products in development, and will therefore maintain positions as dominant players in T1DM over the forecast period,” she notes. “Indeed, technological advances in recent decades have led to the development of improved exogenous insulin therapies, capable of mimicking endogenous insulin activity more effectively. As such, there are several promising insulin products in development, including Novo Nordisk’s NN-1218 and Eli Lilly’s insulin peglispro.”

GBI Research has also identified a strong trend in the pipeline for the development of non-insulin therapies, including adjuvant therapies capable of reducing hyperglycemia in an insulin-independent manner and products attempting to disrupt the pathological immune-mediated destruction of pancreatic beta cells.

“Several of the adjuvant therapies are in late-stage drug development and have demonstrated strong clinical profiles. The emergence of such treatments will drive strong market growth over the forecast period,” Chisholm says, adding: “Additionally, products disrupting the destruction of pancreatic beta cells are likely to have a greater impact on the T1DM treatment algorithms over the longer term.”

**Prostate cancer**

Topping the list for growth, the global treatment market for prostate cancer will expand rapidly from $7.6 billion in 2014 to $13.6 billion by 2021, representing a CAGR of 9.5 percent, GBI reports. That rise, which will occur across the eight major markets of the United States, Canada, France, Germany, Italy, Spain, the United Kingdom and Japan, will be driven primarily by growth in disease prevalence due to an aging global population.

Katie Noon, a senior analyst for GBI, says the continued uptake of Zytiga and Xtandi and the approval of several premium products will also be key factors aiding prostate cancer treatment market growth by 2021.

“Zytiga and Xtandi are both blockbuster drugs, with global sales in 2014 of $2.2 billion and $1.1 billion, respectively. While the strong sales growth of these products is beginning to plateau, it will continue to increase over the next few years,” Noon explains. “In line with this, the approvals of Zytiga and Xtandi in 2013 and 2014, respectively, for the first-line treatment of metastatic castration-resistant prostate cancer patients in Europe and the U.S., and of both drugs for the treatment of docetaxel-resistant patients in Japan, will contribute to the increase in sales of both products.”

The analyst adds that the prostate cancer therapeutics market will also be boosted by the anticipated approval of nine late-stage pipeline products during the forecast period, including the cancer vaccines Prostvac, DCVAC and ProstAtak.

“Novel therapies are expected to be predominantly approved in castration-resistant patients, and to compete with better-established treatments, such as Zytiga, Xtandi and generic docetaxel, or to act as adjuvants to established therapies,” Noon continues. “However, with the likely exception of Prostvac, many of the drugs indicated for use in non-metastatic patients, or in combination with already-costly therapies in metastatic castration-resistant patients, may find that their cost hinders market uptake.”

GBI Research’s report also states that although the therapeutic pipeline for prostate cancer is relatively large, with 448 products in active development, the indication suffers from a high failure rate; however, Noon notes that “the market remains favorable, as this risk is offset by high potential revenue.”
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Collaborating with Chemetics
COPENHAGEN, Denmark—Nuevolution A/S and Janssen Pharmaceutical Companies of Johnson & Johnson, have struck up a multitarget collaboration featuring Nuevolution’s proprietary Chemetics drug-discovery platform. The companies will focus on the discovery and development of new medical entities for the treatment of oncological, infectious and inflammatory diseases, with Nuevolution applying its platform to discover and advance drug candidates against drug targets of interest to Janssen. Though no specific financial details were shared, Nuevolution stands to receive an upfront payment, research funding and milestone payments, if certain research, development and commercial milestones are reached, as well as royalty payments on net sales of commercialized products resulting from this deal.

Ablynx, Novo Nordisk sign drug discovery deal
GHENT, Belgium—An exclusive global collaboration and licensing agreement is now underway between Ablynx and Novo Nordisk for the discovery and development of novel multispecific Nanobody drug candidates in an undisclosed disease area, with an option to expand the agreement to include a second program. Novo Nordisk will pay Ablynx an upfront license fee of €5 million (approximately $5.4 million) as well as up to €4 million (approximately $4.3 million) in research funding in the initial three-year research term of the collaboration. Should Novo Nordisk elect to exercise its option to a second program, it will pay Ablynx an exercise fee of €4 million. Ablynx also stands to receive development, regulatory and commercial milestone payments of up to €182 million (approximately $197.2 million) per program, plus tiered royalties on annual net sales. Novo Nordisk will assume responsibility for the development, manufacturing and commercialization of any products resulting from this collaboration.

Aptose expands oncology pipeline through partnerships
Canadian company links up with Moffitt and Laxai Avanti Life Sciences
BY ZACK ANCHORS
TORONTO—Aptose Biosciences has struck two deals intended to expand the clinical-stage company’s portfolio of epigenetic oncology drug candidates, which targets the underlying mechanisms of cancer. The first agreement establishes a collaboration between Aptose and Tampa, Fla.-based Moffitt Cancer Center that grants Aptose exclusive global rights to develop multi-targeting, single-agent inhibitors to treat hematologic and solid tumor cancers. The second agreement creates a drug discovery partnership with Laxai Avanti Life Sciences (LALS) geared toward developing potential epigenetic drug candidates, including those that arise from the Moffitt-Aptose partnership. Aptose predicts that the partnerships will lead to the discovery of new oncology drugs.

Cracking the code of CFTR
TSRI scientists find crucial disease-specific protein interactions in cystic fibrosis
BY MEL J. YEATES
LA JOLLA, Calif.—Scientists at The Scripps Research Institute (TSRI) have found evidence that a mutant protein (%F508 CFTR) causing most cases of cystic fibrosis acquires disease-specific protein interactions that are responsible for its lack of normal function. Remodeling of these interactions explained rescue of %F508 CFTR function at lower temperature, and allowed the scientists to restore normal function of the mutant %F508 CFTR.

“The proteins and the interactions we’ve identified really fuel the pipeline for new drug targets to treat cystic fibrosis,” said Casimir Bamberger, a research associate in the lab of TSRI Prof. John R. Yates and co-author of the new study with Sandra Pankow, a TSRI staff scientist. Pankow, Bamberger and their colleagues believe a better understanding of a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) could be the key to developing new treatments. Most patients with cystic fibrosis have a mutation called %F508 in the gene that encodes CFTR, which keeps CFTR from folding properly and being processed correctly in cells.

In this study, researchers analyzed cell samples with a tool called Co-Purifying Protein Identification Technology (CoPIT), a new method they developed to identify proteins and analyze data. With CoPIT, they identified almost every protein CFTR interacted with, even tracking the most likely secondary and tertiary protein interactions.

The results were surprising. While it was previously thought that most mutant proteins just lack one or two crucial interactions, the %F508 CFTR mutant had acquired an entirely new disease-specific interaction network. “Three hundred proteins changed their level of interaction, and this was not what we expected,” said Dr. Alvin Shih, head of research and development for Retrophin.

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### CFTR

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...tion, and an additional 200 proteins interacted with the mutated CFTR,” said Pankow. “The process of making membrane proteins is complex and includes many different steps in which CFTR interacts with additional proteins,” Bamberger explains. “Thus there is a set of interactions that normally occurs for non-mutated CFTR. In case of ∆F508 deletion, misfolded CFTR protein is recognized by a different set of interacting proteins that reroute it to premature degradation, for example. In the paper, we show that recognition and rerouting can occur at many different points of the CFTR lifecycle.”

The ∆F508 mutation is a deletion mutation. The researchers’ current understanding is that the loss of phenylalanine 508 prevents correct folding of the transmembrane protein, and thus most of the CFTR protein is targeted for degradation before it even reaches the cell membrane. Based on the interactome, a small percentage of proteins reaches the cell membrane despite the mutation, but does not function properly or is immediately removed from the membrane.

The interacting proteins are not malfunctioning, and neither is the interaction, according to Pankow. They are simply creating a different result. The proteins that interact with the mutated ∆F508 CFTR are different than the ones that interact with the non-mutated CFTR. Additionally, the strength of interaction can be different.

The researchers narrowed these mutant protein interactions to just eight key disruptive proteins, then used a gene silencing approach to remove or “knock down” those proteins when designing their own potent ligand. Temperature shift improves the number of correctly folded and processed CFTR molecules that can eventually reach the cell membrane and improve chloride channel function. This happens at 24–30°C. “Freezing people is not a practical treatment, of course, but this showed us how well this would improve lung function in a patient,” said Pankow and Bamberger.

Interestingly, previous studies have shown that mutant CFTR regains normal function at low temperatures. Temperature shift improves the number of correctly folded and processed CFTR molecules that can eventually reach the cell membrane and improve chloride channel function. This happens at 24–30°C. “Freezing people is not a practical treatment, of course, but this showed us how well this would improve lung function in a patient,” said Pankow and Bamberger.

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**DISCOVERY**

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**TSRI’s Prof. Ardem Patapoutian (right) and research associate Seung-Hyun Woo led a new study on proprioception.**

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Uniquely human gene variants protect older adults from cognitive decline

SAN DIEGO—Many human gene variants have evolved specifically to protect older adults against neurodegenerative and cardiovascular diseases, thus preserving their contributions to society, report researchers from the University of California, San Diego’s School of Medicine in the Nov. 30 issue of Proceedings of the National Academy of Sciences.

“We unexpectedly discovered that humans have evolved gene variants that can help protect the elderly from dementia,” said Dr. Ajit Varki, Distinguished Professor of Medicine and Cellular and Molecular Medicine at the University of California, San Diego School of Medicine. “Such genes likely evolved to preserve valuable and wise grandmothers and other elders, as well as to delay or prevent the emergence of dependent individuals who could divert resources and effort away from the care of the young.”

Varki led the study, along with Dr. Pascal Gagneux, an associate professor of pathology and associate director of CARTA. The researchers discovered that humans have evolved unique gene variants that could help protect the elderly from dementia. Pictured here is the university’s Atkinson Hall.

The standard model of natural selection predicts that once the age of reproduction ends, individuals die. That’s because selection early in life strongly favors variants that benefit reproductive success, even at the cost of negative consequences later in life—one major reason we age, the researchers note. This is indeed the case in almost all vertebrates. Humans (and certain whales) are an exception to this rule, living decades beyond reproductive age. Such elders contribute to the fitness of younger individuals by caring for grandchildren and also by passing down important cultural knowledge. Age-related cognitive decline compromises these benefits, and eventually burdens the group with the need to care for dependent older members. Such elders are a rare and, in humans, unique evolutionary innovation, according to Alvin Shih, the ancestral form of the gene that encodes the CD34 protein. CD34 is a receptor that projects from the surface of immune cells, where it keeps immune reactions in check, preventing “self” attack and curtailing unwanted inflammation.

Researchers at the University of California, San Diego, recently discovered that humans have evolved unique gene variants that could help protect the elderly from dementia. Pictured here is the university’s Atkinson Hall.

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Previous studies suggested that a certain form of CD34 suppresses amyloid beta peptide accumulation in the brain. Amyloid beta accumulation is thought to contribute to late-onset Alzheimer’s disease, a post-reproductive condition that uniquely affects humans and is aggravated by inflammation and cerebral vascular disease.

The researchers compared CD34 regulation in humans and our closest living relatives, chimpanzees. They found that levels of the CD34 variant that protects against Alzheimer’s are four-fold higher in humans than chimpanzees. They also found human-specific variations in CD34 that are involved in the prevention of cognitive decline, such as APOE. The ancestral form of the gene, APOE2, is a notorious risk factor for Alzheimer’s and cerebral vascular disease. But this study finds that variants APOE2 and APOE3 seem to have evolved to protect from dementia. All of these protective gene variants are present in Africa, and thus predate the origin of our species. This finding is in keeping with the valuable role of the elderly across human societies.

“When elderly people succumb to dementia, the community not only loses important sources of wisdom, accumulated knowledge and culture, but elders with even mild cognitive decline who have influential positions can harm their social groups by making flawed decisions,” Gagneux said. “Our study does not directly prove that these factors were involved in the selection of protective variants of CD34, APOE, or both, but it is reasonable to speculate about the possibility. After all, intergenerational care of the young and information transfer is an important factor for the survival of younger kin in the group and across wider social networks or tribes.”

Uniquely human gene variants protect older adults from cognitive decline

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Over the past 12 months, Retrophin, a pharmaceutical company focused on the development, acquisition and commercialization of drugs for the treatment of serious, catastrophic or rare diseases for which there are currently no viable options for patients, has sought to initiate collaborations with patient advocacy organizations and academic institutions to advance drug development in areas of high unmet medical need, according to Dr. Alvin Shih, the company’s executive vice president and head of research and development.

Retrophin and the leadership team of the Grace Wilsey Foundation began discussions to explore a potential discovery collaboration focused on the development of a novel molecular target that may be relevant to NGLY1 deficiency, which resulted in further dialogue on the structure of a potential collaboration.

At the same time, Retrophin was in active discussion with the Warren Family Research Center for Drug Discovery and Development at the University of Notre Dame to explore avenues to collaborate in drug development. NGLY1 had already been identified as a potential area of interest for Notre Dame, so it became clear that a three-way collaboration would be a great way of leveraging each party’s strengths and resources in an effort to find a cure for this devastating disease, Shih said.

NGLY1 deficiency is so nascent, having been described less than five years ago, that there is a limited understanding of the natural history and underlying disease processes, according to sources at Retrophin. These issues are being worked on by academia and the patient advocacy foundations, and will enable drug development to proceed more quickly.

Retrophin brings experience in early-stage drug discovery, including target validation, assay development and compound screening and optimization. The Retrophin R&D team includes experienced senior scientists who have worked on numerous successful drug development campaigns in the rare disease space.

Retrophin will apply its scientific and drug development capabilities to lead efforts towards the validation of a new molecular target. The company will be working hand-in-hand with the Grace Wilsey Foundation and the Warren Family Research Center for Drug Discovery and Development at the University of Notre Dame to advance the science as quickly as possible. “We hope the ultimate product of this collaboration is a transformative therapy for patients with NGLY1 deficiency,” said Shih.

“This collaboration with Retrophin will add momentum to our pursuit of a cure for NGLY1 deficiency. Together, we’ll be able to make a significant impact on the lives of patients and families affected by this condition.”

“This collaboration exemplifies Retrophin’s commitment to working with patient advocacy groups and academic institutions to develop therapeutics for patients suffering from rare diseases,” added Shih. “We appreciate the support from the Grace Wilsey Foundation, which is leading the charge to find a cure for NGLY1 deficiency. Our team is also excited to begin collaborating with the University of Notre Dame, an emerging leader in the rare disease research community.”

Matt Wilsey, president and co-founder of the Grace Wilsey Foundation
Aptose views a multitargeting approach, which incorporates bromodomain inhibition, as an exciting means to enhance efficacy and diminish therapeutic resistance relative to the current landscape in cancer treatment.

William Rice, chairman and CEO of Aptose

“Insights from our work with the MMRF are guiding researchers toward the most likely causes of the disease and targets for drug discovery and development, and are revealing new knowledge about the underlying disease biology in multiple myeloma,” says Dr. Iya Khalil, co-founder and executive vice president of GNS Healthcare.

Aptose's partnership with LALS is of the highest standards, “said Rice. “We knew the MMRF was uniquely positioned to gather the probabilistic causal relationships between variables. REFS begins by reverse-engineering the underlying mechanism that gave rise to the data, to find the most likely explanation, then calculates all possible combinations and outcomes from the data and quickly finds causal relationships and patterns that would otherwise take years to discover. The second component of REFS—forward simulation—enables new insights from the models created in the reverse-engineering step by simulating “what if” questions. The focus is on where the answers converge, which allows predictions about future responses achieved, overall survival, time to disease progression and quality-of-life measures. It is also powered to track treatment data to correspond with genetic information for the individual patient. The combination of cancer epigenetics and genomic translocations (the movement of a chromosomal segment from one position to another, a phenomenon that often occurs in cancer).
While we cover the broad spectrum of pharma and biotech pipelines in these pages, there is no doubt cancer is often a dominating theme. That’s not a problem, of course; we cover the news that seems the most compelling and active, and that’s often in the realm of oncology. Heck, it’s why we have a sister site to our main website called “Cancer Research News” at www.ddncancer.com. That said, though, I’m happy to see that this January issue is pretty varied in terms of therapeutic areas covered, even if oncology is still the single biggest representative.

So, I’ll let oncology dominate my “Editor’s Focus” simply a roundup, let me share some of my own thoughts.

Partly this is because I wanted to draw attention to a statement from the American Society of Clinical Oncology (ASCO), in which ASCO President Dr. Julie M. Vose shared news from a report by the American Cancer Society showing a 23 percent decline in cancer death rates between 1991 and 2012 and that estimated an 1.7 million deaths have been averted as a result—with Vose going on to say: “This 23 percent decline in cancer death rates is the result of decades of advancing our understanding and treatment of cancer. As a result of our nation’s investment in cancer research, we have made tremendous progress in prevention, chemotherapy, surgery, radiation, immunotherapy and molecularly targeted treatments. Every cancer survivor is living proof of its progress.”

“The cancer community cannot afford to let up on its progress. We must capitalize on opportunities to advance precision medicine, innovative patient care through Big Data initiatives and support our nation’s federal research infrastructure through robust funding. If we can meet those needs as a nation, we will continue to see the type of progress highlighted in this report.”

The other reason I wanted to let oncology come out to play in my editorial is because one of our cover articles this month, “FDA beats the averages on approvals,” spends a lot of time talking about how much approval activity had to do with rare diseases, and I didn’t have room in the article to talk about some of the other areas, like cancer.

The FDA noted of 2015 that 16 of the 45 novel new drugs approved in 2015—more than one-third—were designated as first in class. The FDA took a moment to recognize two noteworthy drugs, each in particular notable, and one of whom is Bramce for the treatment of advanced metastatic breast cancer. The other two “noteworthy” drugs were Brivanib to reverse post-surgical neurovascular blockade caused by certain kinds of anesthesia and Praxbind to reverse anticoagulant effects caused by the blood-thinner drug dabigatran.

In addition to the first-in-class and orphan new products, the FDA also called noteworthy the new novel cancer therapies Darzalex, Empliciti, Farydak and Ninlaro to treat patients with multiple myeloma, Alecensa and Targino to treat certain patients with non-small cell lung cancer. Celitocl to treat certain patients with metastatic melanoma, Lonafide for the treatment of certain patients with metastatic colorectal cancer and Yondelis for treatment of soft tissue carcinoma.

And, oh...I can’t help it. Journalistic instincts scream out to balance the scale...the FDA also cited as noteworthy such 2015-approved novel new drugs as Atyvac, to treat complicated intra-abdominal infections and complicated urinary tract infections, and the antifungal product Crescima, to treat invasive aspergillosis and invasive mucormycosis, rare but serious infections. Also notable were the heart drugs Entresto to treat heart failure and Cozaar to reduce hospitalization from worsening heart failure, and the hypercholesterolemia treatments Praluent to treat certain patients with hard-to-treat heterozygous familial hypercholesterolemia and Repatha to treat this same condition as well as homozygous familial hypercholesterolemia. In addition, Viberzi to treat patients who have irritable bowel syndrome with diarrhea, Velatt to treat hyperkalemia and Dabliuz to treat chronic hepatitis C virus genotype 3 infections.

Now, at the core of making this edition of “Editor’s Focus” simply a roundup, let me share some of my own thoughts.

First, it’s great to see such progress in the fight against cancer, both from the research and development front and the regulatory approval front. I imagine cancer will continue to be one of the top killers of people worldwide long past my own demise (hopefully a few decades away, at least), but seeing it get knocked down the list a bit would be good. All forms of death are disheartening, but I think I’d rather see more of them be from lifestyle choices or accidents than from our bodies’ own cells becoming a runaway proliferation train.

Second, I’m pleased to see such progress with approvals at FDA. There have been times in the past I’ve skewed them for sluggish approval rates, but the 2015 news is encouraging both in terms of rare diseases and novel new therapies in general. Here’s hoping that even if we do continue to underfund the FDA (and let’s cut that out, shall we, as well as properly funding NIH) that it can keep the momentum going.

By Jeffrey Bouley, DDNews Chief Editor

Jeffrey Bouley, DDNews Chief Editor

Out of order: Avoiding extremes

It’s no secret that organizations are trying to fool us or control the conversation, but rather that they are passionate about the work they are doing. It’s all too easy to get swept up in the vision and forget or minimize the existing limitations and remaining downstream challenges to turn exciting work into life-altering products and services.

(For the byline, I’d really like you to call me on it if you ever feel I’ve sacrificed my critical eye for pomposity.)

It can be a struggle, however, to find that balance, let alone write it, when researching an article or conducting interviews. It’s not that organizations are trying to fool us or control the conversation, but rather that they are passionate about the work they are doing.

It’s all too easy to get swept up in the vision and forget or minimize the existing limitations and remaining downstream challenges to turn exciting work into life-altering products and services. That’s why it’s so important for me—and any of the other writers and editors at DDNews—to keep a level head while maintaining an open mind.

I noticed an example of this challenge recently while watching a news item about the potential of gene-editing technologies. (For more on these, see Germilines and gene-editing, August 2015 DDNews.)

To listen to the reporter, one would think that all human disease could be cured in the next six months if we just put our backs into it. She kept harping on how precise and accurate CRISPR-Cas9 technology was, implying that it was 100-percent safe, whereas the actual success rates can vary significantly from application to application.

And such rampant expectations tear into the hearts of the real sufferers—the patients and their families desperate for hope. As one distraught mother tearfully pleaded with senators in Washington, “If you have the skills and the knowledge to fix these diseases, then fricking do it.”

The reality and promise of any scientific
COMMENTARY: A VERY BUSY 2016? THE INTERSECTION OF M&AS AND PERSONALIZED MEDICINE

PERSONALIZED MEDICINE DOESN’T dominate the pharma and biotech pipelines, but according to global law firm Reed Smith, it is probably going to exert a huge pull on the direction of merger and acquisition (M&A) activity this year.

According to a new study, “Life lines: Life sciences M&A and the rise of personalized medicine,” 94 percent of life-sciences companies are planning to make an acquisition in the next year, with 93 percent of U.S. respondents expecting these to be cross-border transactions—and more than two-thirds of those are likely to target personalized medicine.

Global law firm Reed Smith commissioned Mergermarket to survey 100 senior corporate executives who reveal the main drivers behind the pursuit of cross-border life-sciences deals, the challenges faced in executing those deals, and how advances in personalized medicine may change the face of the industry.

Despite a continued and current focus on broad indication medicine, personalized medicine offers the promise of higher returns despite smaller potential patient populations given the more targeted nature of drugs.

Looking back at the $164.3 billion in deals in the life-sciences sector just in the first half of last year—an increase of almost 13 percent over the previous year—Reed Smith pointed out such big moves as Teva Pharmaceutical’s $40.5 billion purchase of the generics division of Allergan and noted that the United States saw the lion’s share of deal value in the sector, with 88 U.S.-targeted deals announced in the first half of 2015, worth over $112 billion.

This dealmaking environment isn’t just about big money but is actually “transforming the nature of certain life-sciences companies,” the law firm maintains—Mylan, for example, whose $35 billion bid for Ireland’s Perrigo is likely to result in a company which is currently a manufacturer of generic drugs becoming a diversified healthcare business, and Reed Smith asserts: “There is every reason to expect life-sciences companies to continue to try to reinvent themselves in this fashion ... more than nine in 10 in life sciences businesses (94 percent) currently expect to explore the possibility of an acquisition over the next 12 months—this rises to a full 100 percent for companies whose annual revenue is more than $5 billion.”

Granted, drugs for broad indications continue to drive most pharmaceutical efforts, but this is where the personalized medicine angle comes into play.

In a highly competitive marketplace, where the struggle for differentiation has never been tougher, this broad focus will change, particularly given developments such as sophisticated new data analytics tools, according to Reed Smith’s Diane Frenier, a life sciences corporate partner, who is convinced of the attractions of personalized medicine to many companies in the sector.

“Targeted therapies enable them to differentiate their products with the payers and they’re likely to get better coverage as a result,” she says. “They’re also improving patient compliance—one of the biggest challenges with therapies is that patients don’t take the medication, often because they’re not seeing the benefits, but with targeted therapies, patients are more likely to see a benefit and to comply.”

Despite a continued and current focus on broad indication medicine, personalized medicine offers the promise of higher returns despite smaller potential patient populations given the more targeted nature of drugs—and there are a number of indicators which point to an even brighter future, Frenier asserts, saying: “Businesses are getting more strategic about where they want to focus—they have new, more sophisticated buyers to put to use for shareholders; they’re looking for ways to add value.”

“The future of medicine is to have the right medicine for the right patient and the right dose at the right time,” adds Carol Loepere, chair of Reed Smith’s Life Sciences Health Industry Group.

To see the report and its opinions in their entirety, visit http://dealdimensions.reedsmith.com/life-lines/key-findings

ORDER
CONTINUED FROM PAGE 10

advance, of course, resides somewhere between the hype and the cynicism. And I greatly appreciate the cautionary second-thoughts of many of the people I interview for each of my stories.

When pressed, and often voluntarily, most people acknowledge that science and medicine is a stutter-step rather than a march, that significant strides often terminate in blind alleys and that any true achievement is usually a step in a process rather than the game-changing solution.

We can applaud our efforts while still continuing to challenge ourselves. In fact, this is the only way the system will work. Now, if you’ll excuse me, I have to go watch the greatest hockey team ever to don skates, my beloved Toronto Marlies. Go, Marlies, Go! ✭

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The opinions expressed in guest commentaries do not necessarily represent those of DDNews and/or its owners, editors or other staff.
COLD FACTS
Oregon team refines cryopreservation technique

BY ILENE SCHNEIDER
CORVALLIS, Ore.—A new approach to “vitrification,” or ice-free cryopreservation, could ultimately allow a much wider use of extreme cold to preserve tissues and even organs for later use, according to researchers in the College of Engineering at Oregon State University. If less-toxic cryoprotectants could be discovered, many more applications of vitrification could be feasible, they said. The researchers, whose work was supported by the National Science Foundation, recently announced their findings in PLOS ONE.

Describing the work as “an important step toward the preservation of more complex tissues and structures,” Dr. Adam Higgins, an associate professor in the OSU School of Chemical, Biological and Environmental Engineering at Oregon State University. If less-toxic cryoprotectants could be discovered, many more applications of vitrification could be feasible, they said. The researchers, whose work was supported by the National Science Foundation, recently announced their findings in PLOS ONE.

Dr. Adam Higgins, an Oregon State University professor, and his engineering colleagues believe they have a mathematical model that could be a key tool in using ice-free cryopreservation to allow a much wider use of extreme cold to preserve tissues and even organs for later use.

ATCC says that it has the world’s largest and most diverse collection of human, animal and plant cell lines, as well as molecular genomic tools, microorganisms and biological products.

TOOL & TECHNOLOGY
Osiris FX - CryoJoule Cryopreservation System

MANASSAS, Va.—Aimmed at speeding faster toward a cure for Parkinson’s disease, a chronic, degenerative neurological disorder affecting at least one million people in the U.S., the Michael J. Fox Foundation (MJFF) has selected the American Type Culture Collection (ATCC), a global non-profit biological repository, to provide, for the very first time, vital cell lines to academic, pharmaceutical and biotechnology companies for research.

The MJFF was founded in 2000 by Canadian-born, award-winning actor Michael J. Fox, shortly after he came out about his own Parkinson’s diagnosis. Fox and his band of staffers and volunteers had high hopes that aggressive fundraising and
CRYO
CONTINUED FROM PAGE 12

Engineering expert on medical bioprocessing, explains, “Vitrification as a strategy for cryopreservation has been available for decades and some of the first reports of successful vitrification of mammalian cells were reported about 30 years ago. Since that time, the toxicity of cryoprotective agents (CPAs) used to suppress ice formation has been recognized as one of the major hurdles to achieving successful vitrification, particularly for large samples like tissues and organs.”

While cryopreservation is widely used to preserve semen, blood, embryos, plant seeds and other biological samples, it is limited by crystallization when water freezes and sometimes damages or destroys tissues and cells, according to Higgins. As he explained, “The major challenge with cryopreservation using vitrification methods is that the cryoprotective agents (CPAs) used to suppress ice formation are toxic. Successful vitrification requires selection of CPAs and equilibration of the sample with CPAs in a way that minimizes toxicity. Our mathematical modeling approach helps to identify minimally toxic methods for CPA equilibration.”

The mathematical model developed by OSU engineers is designed to simulate the freezing process in the presence of cryoprotectants and thereby minimize damage. The engineers determined that cells that are initially exposed to a low concentration of cryoprotectant and given time to swell can be vitrified after rapidly adding a high concentration of cryoprotectants. The end result is diminished overall toxicity—healthy cell survival after vitrification rose from about 10 percent with a conventional approach to more than 80 percent with the newly optimized procedure.

Higgins says that vitrification refers to “solidification of a liquid without crystallization,” adding that the resulting vitrified solid is typically referred to as a glass. Vitrification “avoids the damaging effects of ice formation, so it is particularly attractive for cryopreservation of tissues and organs,” he said. “The major challenge with cryopreservation using vitrification methods is that the cryoprotective agents used to suppress ice formation are toxic.”

“The major challenge with cryopreservation using vitrification methods is that the cryoprotective agents used to suppress ice formation are toxic.”
Dr. Adam Higgins of Oregon State University

Higgins says that vitrification “avoids the damaging effects of ice formation, so it is particularly attractive for cryopreservation of tissues and organs,” he said. “The major challenge with cryopreservation using vitrification methods is that the cryoprotective agents used to suppress ice formation are toxic.”

To achieve vitrification, it is necessary to cool and warm quickly enough to “outtrace the ice crystallization process.” The crystallization process is slowed and the freezing point is depressed by addition of CPAs. Therefore, as Higgins says, “the typical strategy is to load the sample with sufficient CPA to enable the sample to be vitrified at the cooling and warming rates that are achievable experimentally.” For large samples, these cooling and warming rates are relatively low, so high CPA concentrations are required.

“Our long-term goal is to apply our mathematical optimization strategy to 3D tissues and organs,” he adds. “This will require refinement of the mass transfer model, among other modifications to the optimization algorithm. While there is still substantial work to do, our recent work shows that our general optimization strategy is effective and lays the groundwork for these future studies.”

Higgins believes that there may be commercial potential as the method is applied to more valuable biological materials, including tissues and organs on a chip. While he believes that the model can help to identify less-toxic cryoprotectants, and ultimately open the door to vitrification of more complex tissues and perhaps complete organs, he noted that nothing the OSU engineers have done to date has intellectual property protection “and our methods and mathematical optimization strategy are publicly available.”

He concludes: “There is still a lot of work to do to realize the full potential of our mathematical optimization approach for designing cryopreservation procedures. With continued funding, I expect we could successfully apply this approach to 3D tissues in a few years, and possibly to organs as well.”

For more information, visit www.DDN-News.com

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Howard Jacob, Ph.D.
Executive Vice President for Medical Genomics and Chief Medical Genomics Officer, HudsonAlpha
Heidi L. Rehm, Ph.D., FACMG
Chief Laboratory Director; Laboratory of Molecular Medicine, Partners Healthcare; Personalized Medicine Clinical Director, Broad Institute; Clinical Research Sequencing Platform; Associate Professor of Pathology, Brigham & Women’s Hospital and Harvard Medical School
Yaron Turpaz, Ph.D., MBA
Chief Information Officer, Human Longevity, Inc.

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Adaptimmune and Universal Cells announce collaboration to develop allogeneic T cell therapies

OXFORD, U.K.—Adaptimmune Therapeutics plc, a leader in the use of TCR-engineered T cell therapy to treat cancer, and Seattle-based Universal Cells Inc., a gene editing company developing universal donor stem cells, today announced that they have entered into a collaboration and exclusive license agreement for the development of allogeneic T cell therapies.

With Universal Cells’ proprietary gene editing technology, Adaptimmune and Universal Cells will exploit their unique strengths to develop affinity enhanced donor T cells that are uni-

versally applicable. The enhanced T cell technology involves selective engineering of TCRs (TCRs and class I and class II HLA proteins), without the use of nucleases, to develop universal T cell products. Adaptimmune and Uni-

versal Cells are planning to develop these off-the-shelf allogeneic affin-

ity-enhanced T cell therapeutics to treat large patient populations.

“This collaboration marks anoth-

er step towards our goal of provid-

ing innovative immunotherapeu-

tics to patients suffering from can-

cer,” said Dr. Helen Tayton-Martin, Adaptimmune’s chief operating officer. “Our proprietary platform for TCR identification, affinity enhancement and safety testing is already best in class, and we set high standards for collaborations. We believe that Universal Cells’ platform for generating universal T cell lines is also best in class and provides us with a great opportu-

nity to test the feasibility of a lon-

ger term allogeneic product, thus allowing a large number of patients to be treated from a single cell line.”

“By partnering with the world leader in TCR engineered T cell immunotherapies, we are poised to develop a scalable, safe and effica-

t product with the potential to revolutionize cancer immunothera-

py,” said Claudia Mitchell, CEO of Universal Cells. “This partnership will combine Universal Cells’ nucle-

a-se-free genome editing platform with Adaptimmune’s unique exper-

tise in TCR engineering to develop a first-in-class therapeutic product based on our universal donor cells.”

Under the terms of the agree-

ment, Universal Cells will grant to Adaptimmune an exclusive, sub-licensable, worldwide license to use, sell, supply, manufacture, import and develop products and services utilizing Universal Cells’ technology within the T cell immu-


notherapy field. Universal Cells will receive an upfront license fee of $3.5 million, and will be eligible for up to $41 million in milestone payments for certain development and product milestones. Universal Cells would also receive a profit-share payment for the first product, and royalties on sales of other products utilizing its technology.

“With growth projections for

new therapies for the millions
der of people worldwide suffering with Parkinson’s.

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ENZYME CONTINUED FROM PAGE 12

produced using avian and mam-

malian tissue-free raw materials, aseptically processed, sterile fil-

tered and highly purified under GMP guidelines. These enzymes are suitable to a wide range of

adipose stem cell, biomedical and bioprocessing applications.

“We are excited to offer

Cytori’s Celase GMP product to

Worthington’s Collagenase and STEMxyme portfolio for bio-

medical research and related bioprocessing applications,” Von Worthington, president and CEO at Worthington Biochemical, stated in a news release.

“With growth projections for

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“With growth projections for
GUT
CONTINUED FROM PAGE 1

Glutathione plays a vital role in the human immune system, enabling nutrient metabolism and regulation of other important cellular dynamics. It is considered to be one of the body’s most powerful antioxidants and the main detoxifying agent in the body. A very small protein, glutathione is produced inside the cells from three amino acids that are obtained either from food or supplementation. Deficiencies of glutathione in the body are known to contribute to oxidative stress.

“Some bacteria in our gut consume glycine, which is required for the synthesis of the glutathione, and imbalances in the composition of the bacteria may lead to the progression of the chronic diseases,” said Mardinoglu.

While Mardinoglu’s study was the first to reveal the role of gut bacteria in regulating glutathione, it has long been known that the makeup of gut microbiota is an important factor in the development of various human disorders, including obesity, type 2 diabetes, atherosclerosis, non-alcoholic fatty liver disease and even malnutrition. Increasing awareness of these dynamics has led researchers to study more closely the interactions between gut microbiota of an individual, the host tissues of the gastrointestinal tract and diet. Independent studies in the past have found that imbalances in the plasma level of glycine as well as other amino acids have been shown to exist in obesity, type 2 diabetes and non-alcoholic fatty liver disease.

Chalmers professor Jens Nielsen noted in a public statement about the new findings that previous studies have found lower plasma levels of glycine in all subjects with certain diseases when compared to the healthy subjects. “In this context, it may be of interest to study the microbial amino acids in the human gut in relation to their potential role in the development of such metabolism-related disorders,” he said.

Researchers working with Mardinoglu confirmed the initial results of the computer-based simulations they used by measuring the level of amino acids in the portal vein of the mice. They also found evidence that gut microbiota regulates glutathione metabolism in the liver and colon as well as in the small intestine. This was indicated by lower levels of glycine that were observed in those organs.

Greater knowledge of how gut microbiota affects health could eventually make it feasible for people to adjust their eating habits in order to create a gut microbiota that is less vulnerable to disease. Nielson suggests that dietary products might eventually be developed for this purpose.

“The discovery that the bacteria in our small intestine consume glycine and regulate glutathione metabolism may lead to the development of food products that can deliver beneficial bacteria (probiotics) to the gut,” he said. Mardinoglu tells DDNews that before any such products are developed—and one could assume pharmaceuticals and biologics could also be developed that might achieve good results—it will be necessary to make more progress identifying gut bacteria and studying more thoroughly the diet required for maintaining the best biomass to maintain a healthy gut microbiome.

“The next step is the identification of the bacteria consuming certain amino acids to see how their abundance changes during the development of the metabolism related disorders,” he says. 

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We look forward to seeing you in New Orleans!
A pair of oncology program presentations

LEXINGTON, Mass.—Biotechnology company Curis Inc. recently announced that its collaborator Aurigene shared preclinical data from two programs AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Those programs included CA-170, a first-in-class oral, small-molecule immune checkpoint antagonist targeting programmed death ligand-1 (PD-L1) and V-domain Ig suppressor of T cell activation (VISTA), and the interleukin-1 receptor associated kinase 4 (IRAK4) inhibitor program. Curis exercised options to license the programs under a collaboration agreement with Aurigene struck earlier this year.

“The collective in vitro and animal model data are very compelling and strongly support testing of CA-170 in human clinical trials in multiple cancers,” said Dr. Ali Fattaey, Curis’ president and CEO. “We are working with Aurigene to complete the IND enabling studies for CA-170 and initiate clinical studies in the first half of 2016.”

Sustained release technology proves effective in vivo

NEW YORK—A preclinical study of Ohr Pharmaceuticals Inc.’s proprietary SKS sustained release technology has yielded positive results for the company. Using an animal model, it was found that sustained supertherapeutic levels of active drug could be reached in target ocular tissues, with a prolonged pharmacokinetic profile. Ohr’s technology uses micro-fabrication techniques to create nano- and micro-particle drug formulations capable of providing sustained, predictable release of a therapeutic drug over a three- to six-month period. The company has four active pipeline programs underway in glaucoma, steroid-induced glaucoma, allergic conjunctivitis and protein delivery for retinal diseases.

“We are extremely pleased and encouraged by the performance of our sustained release platform technology in this in vivo study. The versatility of this delivery technology makes it well suited to deliver hydrophilic or hydrophobic small molecules, as well as proteins with complex structures,” said Dr. Glenn Shlifer, Ohr’s chief scientific officer.

Twice as nice

OncMed’s preclinical comparison study shows improved antitumor, immune responses for bispecific antibody

REDWOOD CITY, Calif.—OncMed Pharmaceuticals Inc. presented new preclinical data for anti-DLL4 combined with anti-VEGF and anti-PD1, a combination targeted toward blocking potent tumor growth while enhancing immune-oncology activity, during the 2015 Society for Immunotherapy of Cancer Conference.

A series of preclinical experiments at the Nov. 9 event compared the impact of an anti-DLL4/VEGF bispecific and a triple blockade of DLL4/VEGF/PD1 on antitumor immune responses. The combination of anti-DLL4/VEGF and anti-PD1 was found to have more potent antitumor and enhanced immune-oncology activity than either agent alone, across a number of measures, according to the post er. The triple blockade of DLL4/VEGF/PD1 significantly inhibited tumor growth with more pronounced tumor regression, while the addition of anti-DLL4/VEGF also improved antitumor activity of anti-PD1 alone in both PD1-responsive and nonresponsive cancers in murine models. These data highlight the ability of the anti-DLL4/VEGF bispecific to combine with anti-PD1 and to modulate antitumor immune responses,” remarked Austin Garney, senior vice president of molecular and cellular biology at OncMed. “In addition to increased antitumor efficacy, we note an enhanced generation of memory T cell responses and reduced tumor-associated macrophages, showing that co-targeting of DLL4 and VEGF with PD1 might be an effective and durable anticancer therapy in part by promoting antitumor immune responses and inhibiting pro-tumor immune responses.”

“DLL4 is a ligand within the Notch pathway and plays important roles in regulating cancer stem cells, tumor angiogenesis and pro-tumor immune responses. On Dec. 11, OncMed presented new data on the development of a novel predictive biomarker for vantictumab at the San Antonio Breast Cancer Symposium, detailing the identification and validation of a novel six-gene signature assay being evaluated as a predictive biomarker of response to vantictumab plus pacitaxel in the treatment of breast cancer. Vantictumab is being studied in three Phase 1b combination clinical trials, including one with pacitaxel in patients with HER2-negative breast cancer. “The research presented today is one example of OncMed’s efforts to identify biomarker early and aggressively that can be evaluated alongside our oncologic therapeutics on the move

Sunesis is advancing its BTK and PD1 inhibitor programs to aid cancer patients

By ILENE SCHNEIDER

SOUTH SAN FRANCISCO, Calif.—Sunesis Pharmaceuticals Inc., a biopharmaceutical company focused on the development and commercialization of new oncology therapeutics for the potential treatment of solid and hematologic cancers, closed 2015 with the presentation of two posters detailing preclinical data from its Bruton’s tyrosine kinase (BTK) and PD1 inhibitor programs at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston.

Sunesis is committed to advancing products to improve the lives of people with cancer. The two poster presentations were titled “SNS-062 is a potent noncovalent BTK inhibitor with comparable activity against wild type BTK and BTK with an acquired resistance mutation” and “PD1 inhibitors SNS-229 and SNS-530 cause pathway modulation, apoptosis and tumor regression in hematologic cancer models in addition to solid tumors.”

“These data represent the first peer-reviewed presentations by Sunesis of our two proprietary kinase inhibitor pipeline programs,” said Dan Swisher, CEO of Sunesis. “Each shows compelling, anticancer activity and a distinct product profile.”

SNS-062 is a non-covalent binding inhibitor of BTK. This target mediates signaling through the B-cell receptor, which is critical for adhesion, migration, proliferation and survival of normal and malignant B-lineage lymphoid cells. BTK has been well validated as a target for treatment of B-cell malignancies, with a BTK inhibitor, Sunesis continued on page 17
SUNESIS CONTINUED FROM PAGE 16

Approved for relapsed/refractory mantle cell lymphoma, relapsed/refractory chronic lymphocytic leukemia (CLL) with deletion and Waldenström’s macroglobulinemia. SNS-062 may provide differentiated opportunities for treatment of B-cell malignancies and other blood cancers. Sunesis plans to file a Clinical Trial Authorization application with the European Medicines Agency to support a Phase 1a study of SNS-062 in healthy volunteers. The rights to develop SNS-062 for oncology indications were in-licensed from Biogen Idec in December 2013.

In January 2014, Sunesis in-licensed a series of PDK1 inhibitors from Millennium that were discovered under a research collaboration agreement between Biogen Idec and Sunesis. PDK1 is a key kinase that is critical for activation of the PI3K/AKT signaling pathway, which is essential for regulating cell growth, differentiation, survival and migration and is frequently activated in cancer. Sunesis has taken a series of PDK1 inhibitors with confirmed antitumor activity in vitro and in vivo into preclinical development and selected two PDK1 inhibitors, SNS-229 and SNS-510, for possible absorption, distribution, metabolism and excretion and safety studies.

There are multiple PI3K pathway inhibitors in late-stage development for use in CLL and solid tumor indications, including breast cancer and pancreatic cancer. Inhibitors of PDK1 are expected to be able to provide similar clinical benefits to those observed with PI3K inhibitors and have the potential to provide additional benefits through inhibition of PI3K independent cancer signaling pathways, especially in cancer types in which PDK1 is overexpressed, such as breast cancer and acute myeloid leukemia (AML). Sunesis’ PDK1 inhibitor can be differentiated from PI3K and PDK1 inhibitors currently in research and development and that may provide novel opportunities for treatment of solid and hematological malignancies, according to the company. “Because PDK1-dependent activation of AKT is critical for PI3K pathway activation, we believe that PDK1 represents a key oncology target within the PI3K pathway,” Swisher tells DDNews. “We believe Sunesis’ PDK1 inhibitors are potential first-in-class compounds with demonstrated inhibition of AKT activity and a compelling in-vitro and in-vivo profile, that have potential for single-agent and broad-spectrum combination activity, thus providing a novel therapeutic opportunity for targeting the PI3K signaling pathway in both solid and hematologic malignancies.”

Sunesis also announced the presentation of results from a Washington University-sponsored Phase 1 trial of its lead drug, vosaroxin, plus azacitidine in patients with myelodysplastic syndrome, and from an analysis of the company’s Phase 3 VALOR trial of vosaroxin and cytarabine in relapsed/refractory acute myeloid leukemia (AML) at the 57th American Society of Hematology Annual Meeting in Orlando, Fla.

QINPREZO (vosaroxin) is an anticancer quinolone derivative, a class of compounds not previously for the treatment of cancer. Preclinical data demonstrate that vosaroxin both intercalates DNA and inhibits topoisomerase II, resulting in replication-dependent, site-selective DNA damage, G2 arrest and apoptosis. Both the U.S. Food and Drug Administration (FDA) and European Commission have granted orphan drug designation to vosaroxin for the treatment of AML. Additionally, vosaroxin has been granted fast track designation by the FDA for the potential treatment of relapsed or refractory AML in combination with cytarabine.

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NanoBio chlamydia vaccine prevents PID in mice

Nanoemulsion adjuvanted vaccines demonstrate positive preclinical results in genital herpes, HIV and chlamydia

BY LLOYD DUNLAP
ANN ARBOR, Mich.—NanoBio Corp., a bio-pharmaceutical company developing and commercializing intranasal and intramuscular vaccines, announced that its intranasal nanoemulsion (NE) adjuvanted chlamydia vaccine has demonstrated efficacy in a traditional mouse challenge model. The study was conducted by leading chlamydia vaccine researchers at the Queensland University of Technology (QUT) in Brisbane, Australia, led by Dr. Kenneth Beagley, professor of immunology and infection.

Chlamydia is one of the most commonly reported sexually transmitted diseases, both in the United States and globally. According to the Centers for Disease Control and Prevention, an estimated 2.86 million infections occur each year. Often referred to as a “silent” infection, estimates suggest 90 percent of women with chlamydia have no symptoms and therefore do not seek treatment. If untreated, a significant percentage of women develop pelvic inflammatory disease (PID) that can lead to lifelong complications including infertility, ectopic pregnancies and chronic pelvic pain. Untreated chlamydia also increases the likelihood of acquiring or transmitting HIV. Currently, there is no vaccine to prevent the spread of the disease.

In 2015, Selecta Biosciences Inc., a clinical-stage biotechnology company developing a novel class of targeted antigen-specific immune therapies using synthetic vaccine particles (SVP), announced a publication in Science describing the use of SVP to create a novel vaccine technology designed to target mucosal tissues. For many chronic and serious infectious diseases that thrive in mucoosa, conventional vaccine approaches have not proven effective for reasons now elucidated in the publication. The new research, by Selecta founders Prof. Ulrich von Andrian and Prof. Omid Farokhzad at Harvard Medical School and Robert Langer at Massachusetts Institute of Technology, further demonstrates preclinical proof-of-concept for an SVP product to prevent Chlamydia trachomatis infections.

In the preclinical study, mice received three administrations of an intranasal NE vaccine and were then subsequently challenged intravaginally with chlamydia. The study’s principal endpoint measured ovudct pathology as an indicator of PID. The results showed that 100 percent of mice receiving no treatment developed oviduct pathology versus just 20 percent of mice receiving the NE vaccine. Animals receiving the NE vaccine generated high levels of both serum and vaginal antibodies (IgG and IgA), strong IL-17 and interferon gamma responses and had faster clearing of the bacteria, as compared to the no-treatment control mice.

“Based on many years of research focused on chlamydia transmission and prevention, our findings indicate that the use of mucosal vaccination provides the best hope for the development of a vaccine to protect against chlamydia,” stated Dr. Kenneth Beagley, professor of immunology at QUT. “The initial study with NanoBio demonstrated exciting results from an intranasal NE vaccine incorporating a generic chlamydia protein. With these results in hand, we are now beginning to test additional chlamydia antigens combined with the intranasal NE adjuvant in mice and larger animals.”

David Peralta, CEO of NanoBio, added, “The results of the chlamydia study further validate the opportunity for intranasal NE vaccines to play a key role in the prevention of sexually transmitted diseases. We have now observed positive results in animal studies for three STDs: genital herpes, HIV and chlamydia. Our research has demonstrated the critical importance of eliciting both mucosal and systemic immunity to protect against some of the most concerning pathogens that enter the body across mucosal surfaces.”

Headquartered in Ann Arbor, Mich., NanoBio is a privately held biopharmaceutical company focused on developing and commercializing vaccines and anti-infective treatments derived from its patented NanoStat technology platform. The company’s NanoStat technology employs a novel oil-in-water NE that can incorporate, deliver and adjuvant multiple antigens. The company’s NanoStat technology employs a novel oil-in-water NE that can incorporate, deliver and adjuvant multiple antigens.

In the Phase 1a clinical trial in patients with advanced solid tumors, brontictuzumab demonstrated single-agent activity in a biomarker-selected refractory patient population. Among 15 patients whose tumors overexpressed the activated form of Notch, eight patients achieved stable disease or partial response, an overall clinical benefit rate of 53 percent. Anti-tumor activity was observed in adenoid cystic carcinoma, colorectal cancer and HER2 negative breast cancer.

A poster presented on Nov. 6 confirmed the antitumor activity of vantictumab, both as a single-agent and in combination with taxane treatment, in a preclinical patient-derived xenograft NSCLC model. Pharmacodynamic biomarkers showed that vantictumab inhibits genes in cancer stem cell pathways that support its mechanism of action. A third poster reported on preclinical studies of OncoMed’s dual-targeting anti-DLL4/VEGF bispecific antibody in xenograft tumor models, which demonstrated superior antitumor activity compared to either anti-DLL4 and anti-VEGF antibodies alone. This combination also showed a greater effect than anti-DLL4 alone in delaying tumor recurrence following the termination of treatment and reducing the frequency of cancer stem cell tumors in the patients, decreased vascular density and demonstrated an improved cardiac profile in cynomolgus monkeys compared to anti-DLL4. **EDITCONNECT: E015163**

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“In preclinical testing, the six-gene biomarker assay has been strongly predictive of antitumor responses to treatment with vantictumab in HER2-negative breast cancers. If these results are corroborated in our ongoing clinical study of vantictumab in breast cancer, it will provide an excellent opportunity to develop a companion diagnostic and target vantictumab use to patients with the highest likelihood of benefit.”

JOHN LEWICKI, executive vice president and chief scientific officer of OncoMed

“We are currently studying our anti-DLL4/VEGF bispecific in a Phase 1a dose-escalating clinical trial,” Gurney continued. “Depending on results from that study, we may consider future combination Phase III in collaboration with our partner, Celgene.”

The data presented at SITC “highlighted that the anti-DLL4/VEGF combination is highly active in preclinical antitumor efficacy studies, including against tumors that respond to anti-VEGF, but not to anti-DLL4,” Gurney said. “Additionally, the data highlighted that the anti-DLL4/VEGF combination can be combined with anti-PD1 to achieve increased antitumor activity.”

“It is notable that we observe activity of the anti-DLL4/VEGF combination against tumors that do not respond to anti-PD1,” he added.

OncoMed researchers also have “observed antitumor activity with the DLL4/VEGF bispecific across a broad range of tumor types in our preclinical studies,” according to Gurney. “These results help shape our understanding of how the DLL4/VEGF bispecific might be able to be paired with anti-PD1 agents.”

The pharmaceutical also presented clinical and preclinical data related to three of its clinical-stage programs at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Data from three posters covered Phase I safety, antitumor and antitumor activity of brontictuzumab, novel biomarker discoveries related to vantictumab in NSCLC and preclinical characterization of safety and efficacy for anti-DLL4/VEGF bispecific.

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John was one of those fortunate few who managed to retire early from his job as an editor, looking forward to spending more time with his grandkids and diving headlong into his hobby of landscape painting. But shortly after retiring, something seemed wrong.

Colors that used to be quite distinct on his palette became muddy and started to lose their luster. He found it difficult to discern the details of a scene. And he began to develop headaches after even the shortest period of reading.

Noticing that he’d avoided his canvases for a couple weeks, his wife finally prodded him and convinced him to see the family doctor…who sent him to an ophthalmologist…who sent him for a battery of tests.

John had age-related macular degeneration (AMD). He was quickly losing his sight in one eye, and was showing early signs of AMD in the other.

Under the scope

AMD is just one of a handful of eye disorders that are seeing increasingly prevalence in the Western world (see sidebar In their eyes on page 22). Although drug therapy and surgery are viable options in some cases, few of these treatments get to the underlying pathology of the diseases. For this reason, researchers are looking more and more to the application of regenerative medicine using stem cells to either bolster the failing ocular tissues or simply replace them with fully functional cells.

“Cellular regenerative medicine for the retina may be the best therapeutic approach when multiple disease processes are causing the degeneration and death of one particular type of cell that is critical for vision,” explains Charles Irving, CEO of Cell Cure Neurosciences. “Multiple disease processes can be difficult to target using a single drug or biologic therapeutic agent.”

Irving’s company is exploring the use of human embryonic stem cells (hESCs) in AMD, differentiating the pluripotent cells into retinal pigment epithelial (RPE) cells to repair the damaged tissues.

“The challenges of this type of ophthalmologic regenerative medicine are to deliver the cells to the proper anatomical site without damaging the cells and the patient’s surrounding tissues, and to have assurance that the cells will survive, engraft and take over the functions of the patient’s own degenerating cells,” he continues.
One key to the use of regenerative medicine in the eye is the fact that the organ is largely immunoprivileged, adds Nianzhen Li, lead scientist for Fluidigm. Effectively an extension of the nervous system, the eye essentially sits behind the ocular equivalent of the blood-brain barrier.

Thus, Li continues, when stem cell-derived tissues are introduced to the eye, there is little risk of rejection. Immunoprivilege makes the eye more amenable to off-the-shelf allogeneic cell therapy. Such an approach should reduce the costs of treatment as therapeutic tissues can be produced in larger quantities and stored. This, in turn, should facilitate reproducibility from at least the product’s perspective.

And nicely, because the eyes occur on the surface of the body and are largely fronted by small windows—whether to the retina or soul—they also provide an accessibility advantage when it comes to tissue replacement efforts. This was noted recently by Kapil Bharti of the National Eye Institute (NEI) and colleagues, who reported on the proceedings of a 2014 meeting convened by the NEI and the National Institutes of Health (NIH) Center for Regenerative Medicine to promote cell-based therapies for disease in the eye.

“Due to its high metabolic activity, it would be very complex to do this in the eye RPE cells from less-diseased areas onto the macular area,” he continues. “Unfortunately, this proved to be a very complex procedure with a high rate of surgical complications.”

“Due to its high metabolic activity, the RPE represents an ideal tissue for transplantation in AMD,” said Elisa Buschini and colleagues at the University of Turin in a recent Clinical Ophthalmology review. “Several strategies, either allogeneic or autologous, have been tried to transplant RPE cells in degenerated areas, without great success due to graft rejection, poor viability of cells and complex attachment to the Bruch’s membrane.”

Thus, although the technical ability to transplant RPE cells was available, clinicians needed a more viable source of tissue.

“There are important advantages to using cells derived from pluripotent stem cell sources, including the ability to have a virtually unlimited supply of cells and to control their differentiation to ensure optimum safety and potency before transplantation,” suggested Schwartz and colleagues.

According to Irving, the first major breakthrough occurred when stem cell researchers noticed clusters of pigmented cells in their cell cultures. The clusters had arisen from the spontaneous differentiation of hESCs into RPE cells.

“However, the real breakthrough came when investigators at Hadassah University Hospital Medical Center in Jerusalem discovered a way to direct the differentiation of hESCs to RPE cells using a particular sequence of differentiation signals,” he recounts.

It was this work that led Cell Cure Neurosciences to initiate a lab-to-bedside translational development program for RPE cells, which the company calls OpRegen.

“OpRegen represents an extension of the early RPE transplantation efforts, but utilizes an external source of RPE cells,” Irving explains.

In September, the company received Fast-Track Designation for OpRegen in AMD and announced it was enrolling patients in a Phase 1/2a dose-escalation and safety study. The trial is currently recruiting patients at the Hadassah University Hospital Medical Center, and Irving expects to announce preliminary results in a few months.

Like OpRegen, most efforts to replace damaged ocular tissue rely on hESCs rather than induced pluripotent stem cells (iPSCs) that are often used in the stem cell arena. From Li’s perspective, this has more to do with history than any other factor.

“hESCs were discovered earlier, so people already have lots of experience,” he concludes.

In wet age-related macular degeneration, the membrane beneath the retina thickens and breaks, triggering angiogenesis, and the newly formed blood vessels, which are easily damaged, exude fluid that further reduces vision.

### Table: Cell source, Company, Disorder, Stage

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Legend: AMD = age-related macular degeneration; hESC = human embryonic stem cell; iPSC = induced pluripotent stem cell; MSC = mesenchymal stem cell. (Source: Clinicaltrials.gov)
REGEN
CONTINUED FROM PAGE 21

ience with it, how know how to grow them and how to differentiate them,” she says. She also, however, acknowledges the totipotent nature of hESCs as a factor, something to which Irving nods.

“If we are going to replace degenerating cells, we might as well replace them with youngest and most robust cells that are available,” he says. “These are usually obtained by differentiating the mother of all cells, the hESC, which remains the gold-standard cell source for regenerative medicine.”

Similar to Cali Cure Neurosciences, Ocata Therapeutics has an early-stage clinical program that is developing hESC-derived RPE cells for the treatment of AMD. Late last year, the company announced that the enrollment of the first patient in its Phase 2 trial that would see three cohorts of up to 20 subjects receive immune suppressive treatment followed by RPE cell transplantation.

“A key goal of this study is to more fully explore the efficacy signal that we reported in the Lancet in October [2014],” with comparison to a control group of untreated patients rather than using the fellow eye for comparison, announced Ocata CMO Eddy Anglade. “We believe that the data developed in this Phase 2 study will allow us to optimize the addressable patient population using well controlled data while assessing potential endpoints for efficacy, safety and immunogenicity.”

In the previous Phase 1 study, Schwartz and colleagues noted that hESC-derived cells were well tolerated for up to 37 months post-transplantation in patients with atrophic AMD and the related Stargardt’s macular dystrophy, without any major signs of adverse proliferation, rejection or adverse events. As well, many patients noted improvements in visual acuity in the treated eye versus its untreated counterpart.

At the same time that the company was announcing progress in its AMD study, it also announced the awarding of an Small Business Innovation Research grant from the NEI and NIH for preclinical development of its photoreceptor progenitor cells for the treatment of retinal degenerative diseases, such as retinitis pigmentosa and photoreceptor dystrophies.

“Dr. Takahashi reported on the progress of multiple animal models that have shown that these cells can integrate into damaged retina, promote survival of host photoreceptors and restore vision in completely blind animals, using either ESCs or iPSCs as source material,” offered Ocata’s chief scientific officer, Robert Lanza.

Beyond embryonic cells

Human ESCs are hardly the only source of tissues for regenerative ophthalmology, however (see Table: Clinical progress on page 21). In late 2015, RIKEN’s Masayo Takahashi reported on the progress of their patient who had received iPSC-derived RPE cells for the treatment of wet AMD, a more advanced form of the disease with an otherwise very bad prognosis. The results come from a clinical trial that was terminated in November.

Takahashi reported the RPE graft was performing well, with no signs of tumorigenesis or recurring neovascularization, and the patient’s showed signs of vision stabilization as well as improvements in visual acuity quality of life.

In the previous Phase 2 trial to evaluate the company’s human neural stem cell platform (HuCNS-SC) in the treatment of geographic atrophy, an advanced form of dry AMD. The trial, designed as a “fellow-eye” controlled study, will see 63 patients aged 50 to 90 years require treatment. The results of HuCNS SC into the eye with inferior best-corrected visual acuity. Patients will be followed for 12 months and monitored for safety as well as structural and functional improvements.

And just a couple months earlier, Henry Klassen and colleagues at the University of California, Irvine, initiated a Phase 1 clinical trial of their retinal progenitor cells (RPCs) in the treatment of retinitis pigmentosa, relying on support from the California Institute for Regenerative Medicine (CIRM). The hope is that the RPCs will protect the photoreceptor cells that have not yet been damaged by the disease and work to replace lost cells.

The work also served as the basis of Klassen’s co-founding of jCyte. “This milestone is a very important one for our project,” said Klassen in announcing the trial, suggesting the group was very excited “to be moving into the clinic after many years of bench research.”

Following a similar pathway to jCyte, UK-based ReNeuron announced in May that it had received FDA approval to commence a Phase 1/2 clinical program to test its RPC platform in retinitis pigmentosa. The open-label dose-escalation study will involve 15 patients of the Massachusetts Eye and Ear treatment center in Boston.

Within weeks, the company also announced the same program had received FDA Fast-Track Designation.

Thus, together with the Orphan Drug Designation already granted for the program in both the United States and Europe, provides accelerated clinical development and marketing authorization processes for our RP treatment candidate, as well as the potential for a significant increase in market exclusivity once approved in these major territories,” said ReNeuron CEO Ovlav Hellebo in the second announcement.

In a nod to ESCs but without the potential ethical baggage, Interna- tional Stem Cell Corp. (ISCO) has gone a completely different route. The company pioneered an alternate native source of pluripotent stem cells derived from unutilized ova, calling the resulting cells human parthenogenetic stem cells.

Using this approach, ISCO has developed methods to generate not only RPE cells for treatment of AMD, but also corneal cells and whole tissues (CytoCor) for use in the treatment of conditions such as corneal blindness. Both programs are in preclinical phases.

Delivering those benefits

In many of the situations described above, cells are injected as a suspension. But there may be times when the cells need to be better organized on a supportive mesh or sheet to deliver optimal efficacy.

“Until recently, no one knew if cells administered as a suspension were capable on settling down and forming the monolayer of cells required for their normal function,” explains Irving. “In that case, some companies decided to skip a cell suspension product and develop a product in which the RPE cells are layered on a prosthetic membrane prior to implantation. We termed such a product OptRegen Plus.”

According to Bharti and colleagues, the choice between cell suspensions and cells in a sheet may come down to a question of how advanced and extensive the disease is.

“In the case of stem cell-derived RPE, cells in a suspension probably function by providing non-polarized trophic support or non-specific phagocytosis,” they noted in Investigative Ophthalmology and Visual Science. “They may provide beneficial effects through the secretion of neuroprotective cytokines or neurotrophic factors and the ability to clear out debris in the subretinal space.”

Thus, even if the new cells don’t integrate into the existing tissues and instead die, they might give the host a sufficient boost in activity to repair itself.

In contrast, cells in a sheet may be required when the tissue damage is more extensive and the host is less likely to self-regenerate. “Cells in a sheet provide polarized trophic support, specific receptor-mediated phagocytosis and vectorial fluid absorption from the apical to basal side. Of course, the cell sheet will have to integrate into the host layer for cells to function over longer periods,” note the
In the case of dry eye syndrome (DES), preliminary results in animal models suggest that topical application may be sufficient. Working in a chemically induced rat model of DES, Emeraldia Beyazid and colleagues in Turkey topically applied mesenchymal stem cells (MSCs) to one eye of each test subject. They then monitored the rats for physiological and symptomatic changes. “Recently, studies have shown that MSCs could play a significant role in corneal epithelial regeneration and transdifferentiate into the corneal epithelial or stromal cells in different types of corneal injury models,” the authors wrote in their Stem Cells International paper.

The researchers noted that MSCs quickly integrated into the host tissue and that signs of inflammation diminished rapidly. “Topically applied MSCs effectively treated DES in rats by reducing inflammation and increasing epithelial recovery that was confirmed by histological and ultrastructural analysis,” they reported.

Bench to bedside

Despite so many cellular platforms entering clinical trials, there are many more programs sitting at the preclinical stage and hurdles remain in making the transition to the clinic. As you move out of research and into the therapeutic space, suggests Howard High, corporate communications fellow for Fluidigm, the need for ultrapure samples that can be easily developed and offer predictable outcomes is increasingly important. “Clinicians and clinical technicians have different skills than their research counterparts, so it is vital—as with any therapeutic modality—that the regenerative medicine system be as technically foolproof as possible,” he said.

As StemCells Inc. board member Alan Trounson told attendees at ISSCR 2014, stem cell researchers and organizations need to shift themselves into monolayers, “Moreover, we expect to obtain imaging data from our clinical studies that indicate that OpRegen cells also do this in dry AMD patients.” Additionally, RPE cells on membranes may find application in patients whose underlying Bruch’s membrane may have been damaged and cannot readily support RPE cells.

At the 2015 meeting of the Association for Research in Vision and Ophthalmology (ARVO), Vladimir Krsticov and colleagues from the NICI reported on their efforts to apply iPSC-derived RPE to biodegradable electrospin PLGA scaffolds of various designs, generating autologous RPE sheets. Using gene expression, immunostaining and electron microscopy, they noted that the RPE cells resembled native cells in morphological and molecular properties. As well, electrophysiological experiments suggested the cells maintained tight contact with neighboring cells. (For other ARVO presentations, see sidebar on the brink.)

Not all applications of stem cell technologies to eye disease require injection or surgery, however. How precisely, these cells are functioning to repair and reverse the damage, however, is still open for speculation.

“Topically applied MSCs can penetrate into conjunctival epithelium and meibomian glands and could decrease inflammation by their anti-inflammatory effects,” they suggested. “This may be mediated by paracrine effects, differentiation or transdifferentiation of topically transferred MSCs to goblet cells or glandular cells, immunomodulatory effects of transferred MSCs or stimulation of repair mechanisms of damaged goblet cells of conjunctiva.” Further studies with larger sample sizes and on different types of DES models are needed to clarify the exact mechanism of how topically applied MSCs show therapeutic effects on DES.

A complex network of neurological (e.g., photoreceptors) and non-neurological (e.g., pigment epithelia) cell types, the retina is a prominent target in regenerative ophthalmology.

Generating iPSC-derived retinal pigment epithelial (RPE) cells from cadavers, Jianmei Saini and colleagues at Rensselaer and University of Albany developed a model system for studying AMD. Gene expression studies showed that iPSC-derived RPE from former AMD patients exhibited significantly higher expression of many markers associated with AMD pathology, including ALP precursor and VEGF-A. Increased ALP and VEGF-A secretion was observed.

Also working in AMD, Daniel Feitelberg and colleagues at Scripps Research Institute and the University of California, San Diego, monitored the longevity and behavior of iPSC-derived RPE in a rat model. Following rats for more than two years post-RPE injection, the scientists detected no increased risk of neoplasms. As well, both immunohistochemistry and flow-cytometry-based phagocytosis assays suggested that iPSC-derived cells that integrated successfully both thrived and functioned normally for up to 2.5 years, while cells that did not integrate were quickly consumed by host macrophages.

Stem Cells International

Outside AMD

Taking a cue from the work done in AMD, Laura Montal and colleagues at Val d’Hebron Research Institute differentiated RPE cells and photoreceptors from hESCs and iPSCs. They then transplanted the RPE cells with or without the photoreceptors into the subretinal space of model rats with retinitis pigmentosa. Monitoring expression markers and using electron microscopy, they noted that the human RPE cells not only survived in the rat eye, but also improved photoreceptor survival and reduced glial stress.

Moving away from pluripotent stem cells, Rui Zhang and colleagues at University Hospitals Eye Institute in Cleveland described their efforts to apply human mesenchymal stem cells (hMSCs) to corneal damage resulting from physical scarring and infection. Working in mice, the researchers treated their subjects with anti-biotic alone, hMSCs alone or both together.

Within days, the corneas of mice receiving combination therapy demonstrated less edema, infiltration and clinical disease than those receiving antibiotics alone, and immunohistochemistry of the same group showed reduced neutrophil recruitment and disruption of the overall structure.

Cell-free

Other researchers demonstrated that it was also possible to receive the benefits of stem cell therapy without the risks associated with the cells themselves. The US National Institutes of Health and colleagues from National University of Ireland, Galway, for example, used ultrasentrifugation and filtration to isolate extracellular vesicles (EVs) from MSCs and examined their efficacy in corneal wound repair. In the presence of MSC-EVs, both corneal epithelial and endothelial cells were observed to migrate to and close scratch wounds in vitro. As well, the treated corneal endothelia demonstrated increased capacity for angiogenesis.

Moving from plastic to animal models, Xiaomin Zhang and colleagues at Tianjin Med University Eye Hospital and University of Louisville applied similarly isolated exosomes from human umbilical cord MSCs to experimental autoimmune uveitis in rats. Treatment significantly reduced the signs of inflammation. Flow cytometry and immunohistochemistry demonstrated similar reductions in the infiltration of T-cells and macrophages.

For more information on EVs and exosomes, see Non-invasion of the body snatchers in the October 2015 issue of DDNews.
Regenerative medicine roundup

A quick look at several other companies involved in various therapeutic applications of cell therapies

New funding for cell-based hemophilia therapy

LONDON, Ontario—A new research grant of $8.5 million (Canadian dollars) awarded by the European commission via its Horizon 2020 program aims to address patients affected by hemophilia A, as well as factor VIII deficiency. The funds are earmarked to the HemAcre consortium, consisting of Canadian-based Sernova Corp. and five European academic and patient groups who will be working jointly to advance development of a GMP clinical-grade factor VIII-releasing therapeutic cell product via Sernova’s signature human pluripotent stem cell platform. “This funding will enable us to begin expanding toward commercialization of our cell products,” said Joerg Schippert, chief executive officer of Sernova.

ISC0 cleared to initiate trial of stem cells for treatment of Parkinson’s

CARLSBAD, Calif.—Moving outside the area of ophthalmology in regenerative medicine, International Stem Cell Corp. (ISCO), one of the sources for this special report, announced in December that the Therapeutics Goods Administration of Australia cleared a regulatory submission of ISCO’s wholly owned subsidiary, Cyto Therapeutics, to initiate a Phase 1 clinical trial, a dose escalation trial of human partheno- genetic stem cells-derived neural stem cells (ISC-hpNSC) in patients with moderate to severe Parkinson’s disease (PD). Currently, there is no cure for PD, which is the second most common neurodegenerative disease and affects over 7 million people worldwide.

“With this achievement we have advanced to the final stages of clinical development to treat Parkinson’s disease,” said Michael R. McConnell, CEO of ISCO. "Our product, ISC-hpNSC, is designed to provide a neurological benefit for those suffering from Parkinson’s disease. We believe that ISCO-hpNSC has the potential to transform the lives of patients suffering from this debilitating disease.”

The therapy being developed by the HemAcre consortium is expected to be highly disruptive to the current standard of care treatments for hemophilia A. The therapeutic uses the patient’s own cells, which have been corrected for the factor VIII gene. Central to the therapy is Sernova’s Cell Pouch System, a novel, implantable and scalable medical device that would release factor VIII on a continual basis at a rate that would be expected to significantly reduce disease-associated hemorrhaging and joint damage. The consistent delivery of factor VIII is also expected to reduce or eliminate the need for multiple weekly infusions which is the current standard of care using plasma-derived or recombinant, genetically engineered factor VIII for the prophylactic treatment of hemophilia A.

Pluristem reaches agreement with Japan’s PMDA

HAIFA, Israel—Pluristem Therapeutics Inc., a developer of placenta-based cell therapy products, announced in mid-December that it has reached an agreement with Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) on the design of the final trial needed to apply for conditional approval of PLX-PAD cells in the treatment of critical limb ischemia (CLI). The approval of the protocol for the 75-patient trial was part of a larger agreement on the development of PLX-PAD via Japan’s new accelerated regulatory pathway for regenerative medicine.

“We are very encouraged that we have advanced our strategy to expedite commercialization of our cell products. Pluristem is now positioned favorably to accelerate negotiations with those Japanese pharma companies interested in becoming dominant players in the expanding regenerative medicine market in Japan,” stated Pluristem Chairman and CEO Zami Aberman.

Patients will be randomized into three groups of 25. Group one will receive an initial 150 million PLX-PAD cell dose followed eight weeks later by a second 150 million cell dose and a third dose 8 weeks after that, treated with an initial 300 million PLX-PAD cells followed eight weeks later by a second dose of 300 million cells and group three will receive two doses of placebo. The primary efficacy endpoint will be a CLI-free diagnosis of a patient for 60 days.

Ground-state stem cells hold promise for genetic therapy, study finds

DURHAM, N.C.—A new study appearing in STEM CELLS Translationl Medicine shows that ground-state, patient-specific induced pluripotent stem cells show significant promise for disease modeling, gene editing and future therapeutic applications. Ultimately, the discovery by a Chinese research team could lead to improved treatment for genetic diseases such as beta thalassemia, a blood disorder caused by flawed or missing genes.

Scientists conducting the study derived the induced pluripotent stem cells (iPSCs) in a ground state, using a novel, implantable and scalable medical device that would release factor VIII on a continual basis at a rate that would be expected to significantly reduce disease-associated hemorrhaging and joint damage. The consistent delivery of factor VIII is also expected to reduce or eliminate the need for multiple weekly infusions which is the current standard of care using plasma-derived or recombinant, genetically engineered factor VIII for the prophylactic treatment of hemophilia A.

Scientists’ findings advance understanding of human cell behavior

The immediate suspension of the Radiate study of chronic spinal cord injury required some difficult choices, including the suspension of patient enrollment and service agreements. This decision, a result of preliminary study findings, was determined to be necessary as a result of the potential for future harm and the need to eliminate risk to participants. The immediate suspension of the Radiate study followed the arrest of a former StemCells staff member by law enforcement and the suspension of patient enrollment and service agreements.

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Top-line data released on Phase 3 linaclotide trial

TOKYO & CAMBRIDGE, Mass.—The Phase 3 clinical trial of linaclotide, being conducted in Japan in adults with irritable bowel syndrome with constipation (IBS-C), has met its primary endpoints, Astellas Pharma Inc. and InmuneX Pharmaceuticals Inc. announced recently. Linaclotide is a guanylate cyclase-C (GC-C) agonist currently approved in the United States for the treatment of adults with IBS-C and chronic idiopathic constipation (CIC). Top-line data from the trial indicate that patients treated with linaclotide showed statistically significant improvement compared to placebo-treated patients for both of the two co-primary endpoints.

"Linaclotide has now met all primary endpoints in all eight of its Phase 3/2b clinical trials, spanning two indications, three doses and multiple countries," noted Dr. Mark Currie, chief scientific officer and president of research and development at InmuneX.

Phase 1 progress for Actimab-A

NEW YORK—Data from the Phase 1 portion of Actimab Pharmaceuticals Inc.'s Phase 1/2 clinical trial of Actimab-A were shared at the 57th American Society of Hematology Annual Meeting. Actimab-A is being studied in acute myeloid leukemia (AML) patients over the age of 60 that have not received prior therapy and have declined or are unsuitable for intensive induction chemotherapy. Eight of 11 patients had maintained or improved blast reduction of 72 percent. Four of 14 patients presented with objective responses after one cycle of therapy with one achieving complete remission, two achieving complete remission with incomplete platelet count recovery and one achieving complete remission with incomplete blood count recovery. The rate of remission and tolerability results seen with Actimab-A in this trial are very encouraging, as elderly patients diagnosed with AML have limited options and prognosis is typically poor," said Dr. Joseph Junct, study investigator at Columbia University Medical Center.

Initial data for IMO-8400

Idera Pharmaceuticals reports positive data from ongoing Phase 1/2 clinical trial of toll-like receptor antagonist in patients with Waldenström's macroglobulinemia

BY LLOYD DUNLAP

ORLANDO, Fla.—Idera Pharmaceuticals Inc., a clinical-stage biopharmaceutical company developing toll-like receptor and RNA therapeutics for patients with cancer and rare diseases, has presented initial clinical data from its ongoing Phase 1/2 clinical trial for IMO-8400, a Toll-like receptor (TLR) 7, 8 and 9 antagonist, being evaluated for the treatment of patients with relapsed or refractory Waldenström's macroglobulinemia (WM). These results provide evidence that IMO-8400 has clinical activity and is well tolerated. The results were presented during a poster session at the 57th Annual Meeting of the American Society of Hematology in Orlando, Fla.

"Our clinical trial in Waldenstrom's macroglobulinemia represents the first step in our understanding of the potential role that TLR antagonism could play in B-cell malignancies," said Dr. Dov Tamarkin, CEO of Idera.

Relief in sight with FDX104?

Phase 2 data is positive for Foamix’s acneiform rash treatment

BY KELSEY KAUSTINEN

REHOVOT, Israel & BRIDGEWATER, N.J.—Clinical-stage specialty pharmaceutical company Foamix Pharmaceuticals Ltd. closed the year with the release of top-line results from its Phase 2 clinical study of FDX104, a topical foam containing 4 percent doxycycline. The compound is being advanced for the prevention of moderate-to-severe skin rashes in patients treated with epidermal growth factor receptor antibody inhibitors (EGFR) cetuximab (also known as Eribulin, marketed by Eli Lilly) or panitumumab (Vectibix, marketed by Amgen) for head and neck and colon cancers, among others.

EGFR is often overexpressed or dysregulated in several types of solid tumors, including gastrointestinal tumors, and therapeutics targeting the EGFR-mediated signaling pathway are becoming a leading tactic for treating advanced lung, head and neck and colorectal carcinoma. However, even though EGFR inhibitors have been
Survey reveals majority of life-sciences companies lack automated processes

Industry leaders are adopting ‘best of breed’ applications in eClinical stack to speed clinical trials

BY LLOYD DUNLAP

SAN FRANCISCO—Preliminary findings from the goBalto Inc. 2015 Global Study Startup Survey uncovered significant gaps in the industry’s ability to efficiently manage document workflows and activities associated with starting clinical trials.

The survey found that industry leaders were continuing to adopt ‘best of breed’ cloud-based eClinical solutions, such as clinical trial management systems (CTMS), electronic data capture (EDC) and electronic trial master file (eTMF); however, even the latest releases of these applications fell short in addressing one of the most inefficient and costly bottlenecks of clinical trial conduct—study startup (SSU).

The process of initiating clinical trials continues to remain cumbersome, challenging and often behind schedule, making SSU one of the poorest-performing aspects of clinical trials. “Excel is still the mainstay in managing clinical trials, and while a few have tried to use existing eClinical or document management systems for SSU, they have fallen short,” said Supaj Jadhav, goBalto’s CEO. “Only a purpose-built SSU solution capable of handling complex regulatory/SOP workflows is able to tackle the complexities associated with starting clinical trials, providing true efficiencies via cycle time reductions.”

Unfortunately, the use of Microsoft Excel is still omnipresent. Over two-thirds of sponsors and CROs use Excel for site selection and evaluation, with the majority of sponsors (93 percent) and CROs (86 percent) using Excel for site feasibility. Moving further into the clinical study life cycle, activation, over 80 percent of sponsors and CROs still use Excel for tracking of SSU processes. Ironically, three of the top sponsors/CRO pain points were directly related to the limitations of using Excel for SSU, namely lack of operational oversight with no availability of real-time reporting on clinical trial status (or CRO performance), lack of project management standards (particularly for activities impacting milestones along the critical path) and lack of integration of systems for site selection, feasibility, activation and documentation management.

When asked about the reasons for this enduring situation, goBalto’s founder and president of business development, Jae Chung, is frank: “Companies are encumbered by their spreadsheets, but goBalto’s cloud-based system is like TurboTax. And many people [and companies] are averse to change.”

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malignancies, specifically in those harboring the MYD88-L265P oncogenic mutation which is highly prevalent in Waldenström’s macroglobulinemia,” stated Vincent Milano, Idera’s CEO. “We are pleased that the initial results from this ongoing trial met our objectives in determining safety and tolerability, as well as clinical activity of IMO-8400 in this patient population. We are further encouraged that the safety profile seen to date will enable us to expand this study to evaluate higher doses of IMO-8400.”

The results reported by Idera Chief Medical Officer Dr. Joanna Horobin are from 15 evaluable patients with WM who had a history of relapse or failure to one or more prior therapies and who completed at least one cycle of therapy with IMO-8400. Patients enrolled in the multi-center, open-label, dose ranging clinical trial which evaluated three dose levels of IMO-8400 (0.6 mg/kg weekly, 1.2 mg/kg weekly and 1.2 mg/kg twice a week) administration for a period of up to 24 weeks. The primary objectives of the study were to assess safety and tolerability, with secondary objectives of assessing clinical activity, pharmacokinetics and defining the optimal dose for further clinical evaluation. In addition to clinical treatment parameters, cytokine levels were analyzed as an exploratory endpoint in the trial.

IMO-8400 was generally well tolerated at all dose levels studied. The maximum tolerated dose of IMO-8400 has not yet been identified. Across all dose cohorts, six of 15 patients (40 percent) with relapsed or refractory WM had an objective response. Three responders were refractory toibrutinib.

In the highest dose cohort, 1.2 mg/kg twice a week, three of six patients (50 percent) had an objective response and two had stable disease. The median time to first response was ~10.5 weeks.

There was improvement in bone marrow findings, hemoglobin and disease symptoms.

An exploratory analysis showed a significant correlation between change in M-protein and a change in IL-10, with decreases in IL-10 being seen in responding patients.

In summary, Milano stressed in a follow-up teleconference, these data in patients with WM provide the first clinical evidence supporting inhabitation of the TLR pathway as a potential therapeutic approach for B-cell malignancies characterized by the MYD88 L265P oncogenic mutation. Evaluation of higher IMO-8400 dose levels is planned.

Waldenström’s macroglobulinemia is a rare and slow-growing form of B-cell lymphoma with approximately 5,000 to 15,000 new cases diagnosed in the United States each year. The median age at diagnosis is between 60 and 70 years of age, and symptoms include fatigue, night sweats, headaches, visual problems, pain and abnormal bleeding due to complications such as anemia, retinopathy and peripheral neuropathy. Approximately 90 percent of WM patients present with the MYD88 L265P oncogenic mutation. TLRs are receptor proteins that play a central role in the innate immune system. In healthy individuals, TLRs recognize invading pathogens and endogenous molecules released from damaged or dysfunctional cells, and initiate signaling cascades that trigger an inflammatory response. Through these signaling cascades, TLRs are involved in activating the adaptive immune system, in which B-cells play a critical role. Based on its proprietary chemistry-based discovery platform, Idera discovered and is developing IMO-8400, which has demonstrated activity in multiple preclinical models of cancer and autoimmune disease.

Idera’s proprietary technology involves using a TLR-targeting technology to design synthetic oligonucleotide-based drug candidates that act by modulating the activity of specific TLRs. In addition to its TLR programs, the company is developing a third-generation antitumor antigen to target that it has created using its proprietary technology to inhibit the production of disease-associated proteins by targeting RNA.

For more information, visit Idera’s clinical trial website at www.imontrail.com.

**EDITCONNECT: E011619**

**FOAMIX CONTINUED FROM PAGE 25**

shown to be effective in treating a variety of skin conditions, the most common side effects, occurring in between 49 and 95 percent of patients, are severe acne-like rashes on the face and upper trunk.

So far, there are no approved treatments for this issue, also known as acneiform rash, though some benefit has been seen through treatment with minocycline and doxycycline, as well as topical therapies. These can also result in systemic side effects, however, and potential drug-drug interaction with the primary oncology treatment.

“Acleriform rash is the most noticeable side effect of EGFRi drugs. In many cases, it is necessary to interrupt treatment to manage these side effects,” said Dr. Einat Shacham-Segal, head of the Gastrointestinal Oncology Unit at the Sheba Medical Center in Israel and a principal investigator in the study. “The ability of FDX104 to reduce the incidence and severity of such rash is impressive and promising. We currently don’t have an effective treatment for this side effect, which is especially disturbing and disruptive to this population.”

This study, consisting of 24 patients, focused on assessing the safety and efficacy of FDX104. The patients acted as their own control, treating one side of their face with FDX104 and the other with the matching foam vehicle (placebo). The results demonstrated a statistically significant effect of the foam in reducing the severity of the acneiform rash, with the FDX104-treated side displaying a lower severity of the rash than the placebo-treated side. Severity was assessed in two ways: one, photos were taken at each study visit for an independent dermatologist to grade at the end of the study; and two, study investigators assessed severity using a modified MASCC EGFR Inhibitor Papulopustular Eruption Grading Scale. The foam appeared to be safe and well tolerated, with no drug-related systemic adverse events. While local reactions presented in six patients, all six cases were mild, and five resolved before the end of the study.

“The results of this unblinded study need for a safe and effective treatment for egfr-induced rash, and we are pleased with the results of this clinical study,” Dr. Don Tamarkin, CEO of Foamix, commented in a press release. “FDX104 has the potential to improve patients’ quality of life and help maintain patients on their optimal anti-cancer treatment. We are dedicated to developing best-in-class medicines that can have a positive impact on patients’ lives.”

Brian Orelli of The Motley Fool remarked that the next step for FDX104 will likely consist of a Phase 3 program before it will secure regulatory approval, noting that “Like all small Phase 2 trials, the biggest risk is that the efficacy difference between FDX104 and placebo isn’t seen in a larger trial.” He adds that there is a potential for side effects to be identified in a larger patient population, but pointed out that FDX104’s active ingredient, doxycycline, “is a common antibiotic that’s sometimes use as an oral off-label treatment for the rash, so it’s probably a low risk.”

“Investors in Eli Lilly and Amgen should keep an eye on the development of FDX104, because the companies will obviously benefit if FDX104 can help keep patients on their drug longer,” he concluded.

**EDITCONNECT: E011616**

**FOAMIX CONTINUED FROM PAGE 25**

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- **IONSet™/JIONCore™** - Ligand-gated and voltage dependent ion channel-directed
- **KINAset™/KINACore™** - Based on pharmacophores derived from known kinase actives
- **GPCR™** - Beta-turn mimetic scaffolds
- **NHRCore™** - Nuclear hormone receptor-directed
- **Fragment Library** - Rules of 3 biased compounds

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**CLINICAL TRIALS**

**CONTINUED FROM PAGE 25**

**“Our clinical trial in Waldenström’s macroglobulinemia represents the first step in our understanding of the potential role that TLR antagonism could play in B-cell malignancies, specifically in those harboring the MYD88-L265P oncogenic mutation which is highly prevalent in Waldenström’s macroglobulinemia.”**

Vincent Milano, CEO of Idera

**IDERA**

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**CLINICAL TRIALS**

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**CORE Library** - More than 575,000 compounds based on novel, sp3-enriched designs
- **EXPRESS-Pick™** - More than 460,000 druglike compounds

> **DIVERSITY LIBRARIES**

- **DIVERSet® Libraries** - Diverse chemical structures with broad pharmacophore coverage
- **PremiumSet™** - Diverse compounds with high-scoring chemical features
- **CombSet** - Selection of CORE Library compounds with built-in SAR
- **MicroFormat** - Representative selection from EXPRESS-Pick

> **TARGETED LIBRARIES**

- **CNS-Set™** - Increased probability of oral bioavailability and blood-brain barrier penetration
- **IONSet™/JIONCore™** - Ligand-gated and voltage dependent ion channel-directed
- **KINAset™/KINACore™** - Based on pharmacophores derived from known kinase actives
- **GPCR™** - Beta-turn mimetic scaffolds
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**IDERA**

**CONTINUED FROM PAGE 25**
Epigenomics reports high sensitivity for biomarker panel

BERLIN & GERMANTOWN, Md.— The recent Association for Molecular Pathology 2015 Annual Meeting saw Epigenomics AG sharing promising data from a study applying a proprietary panel of blood-based DNA methylation biomarkers for the detection of lung cancer. The panel, which includes the SHOX2, FOXD2 and PTGER4 genes, was compared with two proteins commonly cited for the detection of lung cancer. The panel, which actively spread cancer to new sites in the body, provides insights into how existing medications work. Furthermore, knowing which resistant cancer subclones are present allows for better triaging of patients into personalized therapies right from the start.

“Successful treatment of cancer depends on understanding the heterogeneity of the patient’s tumor burden and the driving genetic alterations behind disease progression,” said Murali Prahalad, president and CEO of Epic Sciences. “Research conducted at the Abramson Cancer Center will enable faster development of novel personalized treatments that are able to address this heterogeneity.”

But the deal-sealer perhaps for the Abramson Cancer Center was in seeing Epic Sciences’ no cell left behind CTC detection and characterization platform, used to quantify the proteomic and genomic changes that accumulate in tumor cells over time and in response to successive rounds of therapy. Following a simple blood draw, the Epic Sciences platform can reportedly detect all categories of CTCs in the blood and identify, on a single-cell basis, subpopulations of metastatic cancer cells that may be resistant or susceptible to cancer therapeutics.

Ryan Dittamore, vice president of marketing and translational research for Epic Sciences, in explaining his company’s new partnership with the Penn Medicine Abramson Cancer Center.

In the next few decades.

Such research is important, he says, “because a patient’s tumor can have heterogeneous subpopulations of cancer cells, each with distinct genomic variations and protein expression,” he said. “Some of these subpopulations must be targeted with a more effective therapy.”

Precision medicine unleashed

Whole-exome sequencing test reveals untapped therapeutic options

BY ILENE SCHNEIDER

NEW YORK—“Most tests are more appropriate for untreated or localized cancers,” explains Dr. Mark Rubin, director of the Englander Institute and the Homer T. Hirst III Professor of Oncology in Pathology at Weill Cornell Medicine, vice chair for molecular and genomic pathology at NewYork-Presbyterian Hospital and head of the precision medicine program at both institutions.

“Our test helps to anticipate mutations once a patient has undergone treatment, to help determine the next course of action,” Rubin and his colleagues asked themselves what would be the best kind of genetic testing for advanced cancer. They decided that whole-exome testing captured the whole protein coding area to determine all possible mutations.

The EXACT-1 test can reveal untapped therapies for patients with advanced cancers by PRECISION CONTINUED ON PAGE 29

Institutions and researchers within the Weill Cornell Medicine family developed the EXACT-1 test to identify alterations within tumors—some of which drive cancerous growth—on a magnitude up to hundreds of times greater than similar technologies. Pictured here is one of the newest Weill Cornell facilities, the Belfer Research Building.

VeCTRA DA making waves in RA

Crescendo shares data highlighting the test’s ability to better depict disease activity

BY KELSEY KAUSTINEN

SOUTH SAN FRANCISCO, Calif.—Roughly 1.5 million people in the United States alone suffer from rheumatoid arthritis (RA), an autoimmune disease that affects the linings of joints, causing pain and swelling that can lead to bone erosion. Crescendo Bioscience, a molecular diagnostics company developing and commercializing quantitative blood tests for RA and other autoimmune diseases, is advancing Vectra DA, a multibiomarker blood test for rheumatoid arthritis, in hopes of leading to better treatment options for patients with RA. The company has conducted VECTRA CONTINUED ON PAGE 29

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assessed individually through
immuno-fluorescence for morphol-

ogy and protein markers.”

“Cells of interest can subse-
quently be individually isolated and analyzed or single cell
sequencing.” Dittamore notes. “These CTC profiles can then be
used to generate signatures that are the basis of companion diagnos-
tics that can identify patients to the right therapies.”

A primary research goal in onco-
lology is the concept of cellular hetero-
gen, by which is a very important
to science at the time. This has a
highly saturated patient population.

In a recent study, the precision medicine team reviewed
the data and generated reports that summarize the key clinical and genetic findings. The precision medicine team reviews
the results and consults with the patient’s oncologist to determine if a Vectra DA score could be used to predict an optimal
choice of second-line treatment for 157 patients with RA that were
MTX incompleter responders. The results showed that in patients with
early RA, a low Vectra DA score in incomplete response to MTX, the Vectra DA
score could predict the relative efficacy of second-line treatment with
triple therapy versus anti-TNF.

“Predicting response to drug therapy is an important goal for per-
sonalizing treatment for individuals with RA,” commented Dr. Ronald
F. van Vollenhoven, director of the Department of Medicine at the Karolinska
Institute in Stockholm, Sweden, and the study’s lead investigator. “In
this study, patients with a low Vectra DA score were more likely
to respond to conventional triple therapy than to anti-TNF therapy.
These findings may help facilitate and improve the development of
personalized and cost-effective treatment plans for patients with RA.”

In another study, this one evaluating Vectra DA’s ability to predict
disease relapse in patients with RA in sustained remission following
the tapering of treatment with disease-modifying anti-rheumatic drugs,
the test improved the prediction of relapse and, when com-
pared to current clinical practice, was able to identify patients who would be better
assessed for a novel cell type or biomarker.

Dr. Elena Hitraya, chief medical officer at Crescendo. In addition, she notes, RA is a very heterogeneous
disease, with a variety of growth factors and cytokines playing a role
in disease development. The fact that Vectra DA combines a
diversity of cancer types, with a variety of growth factors and cytokines playing a role
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A cancer antibody with more punch

ProBioGen AG, a specialist in contract development and manufacturing of complex glycoproteins, and Vancouver, British Columbia-based Zymeworks Inc., a global antibody therapeutics development company, have signed an agreement under which ProBioGen will complete cell line development of a Zymeworks bispecific antibody product candidate, applying its GlymaxX technology to enhance antibody-dependent cell-mediated cytotoxicity (ADCC).

According to an NIH-authored article carrying the provocative and hopeful subhead “Light at the end of the tunnel,” with 23 approvals in the United States and other countries and four approvals outside the U.S., antibodies are now widely recognized as therapeutic molecules. “The therapeutic and commercial successes met by rituximab, trastuzumab, cetuximab and other mAbs have inspired antibody engineers to improve the efficacy of these molecules,” said ProBioGen’s chief scientific officer, Dr. Volker Sandig, commenting: “We have been working productively with Zymeworks for some time already and look forward to contributing to the success of Zymeworks’ Azymetric bispecific antibody platform. Our proprietary CHO expression platform is ideally suited for the expression of bispecific antibodies with high purities and expression titers. The implementation of our innovative GlymaxX technology for enhancing the efficacy of this therapeutic candidate.”

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ReproCELL not only noted its acquisition of Scotland-based Biota “as aimed at strengthening the pharmaceutical industry-targeted drug discovery support aspect of our business, which is one of the mainstays of our company.”

ReproCELL Group company, for the past five years, which has helped us establish a very successful U.S. subsidiary. We see the acquisition as the natural next step in the growth of the U.K. and U.S. businesses.”

ReproCELL acquired life-sciences CRO Biopta

BY KELSEY KAUSTINEN

GLASGOW, U.K. — ReproCELL Inc., a Japanese regenerative medicine company, recently acquired Scottish life-sciences company Biota and its U.S. subsidiary Biota Inc., in a deal that was slated to be completed in Dec. 10. Following the transaction, Biota will continue operations from its Glasgow headquarters, with plans to expand its workforce to 30 employees over the next three years. An immediate investment is expected to be made to expand Biota’s range of contract research services. No financial details for the deal were released.

“The acquisition by ReproCELL is a great opportunity to build on the solid platform we have in outsourced drug discovery services,” Dr. David Bunton, Biota’s co-founder and CEO, said in a press release. “Scotland is known for the quality of its scientists and customer service, and ReproCELL’s investment recognizes these strengths. We have had a close partnership with BioServe, another

Xcelodose boosts Juniper Pharma’s CDMO offerings

NOTTINGHAM, U.K. — Juniper Pharma Services recently announced the expansion of its Xcelodose powder micro-dosing system as part of its suite of GMP capabilities. Xcelodose allows Juniper to accurately fill API directly into capsules to primarily support first-in-human studies, reduce formulation requirements and minimize drug substance wastage. It also enables automated processing of API directly into capsules at very low doses, offering an ideal approach for highly soluble products and potent molecules.

Clare Madden-Smith, senior vice president at Juniper Pharma Services, said: “The increased usage of Xcelodose is a natural expansion of our manufacturing services. Encouragingly, the service is already helping satisfy the growing needs of our clients to get to clinical trials as quickly as possible without compromising on quality. The technique simply allows us to make and supply batches of the drug in capsules for clinical use in a much more precise and economical manner.”

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Two for Tissues

Zymeworks contracts ProBioGen for bispecific GlymaxX antibody cell line development to enhance ADCC potency of antibody

BY LLOYD DUNLAP

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Dr. Ali Tehrani, president and CEO of Zymeworks

“Our productive partnership with ProBioGen and their highly skilled team will help advance one of Zymeworks’ therapeutic programs into the clinic. The incorporation of the GlymaxX technology is one of the key components in enhancing the efficacy of this therapeutic candidate.”

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“We believe that biotherapeutics developed using the Azymetric platform have the

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For more information, visit www.DDN-News.com
Company’s second office in the region will strengthen customer relations and help develop new business among emerging and established Japanese companies.

BY LLOYD DUNLAP

TOKYO & RAVENSBURG, Germany—Vetter, one of the global leaders in the aseptic manufacturing of drug-delivery systems servicing the top 10 pharma/biotech companies worldwide along with mid-size firms and emerging groups, has announced the opening of a new business entity in Tokyo. The announcement of the new Japanese office was made toward the end of 2015 at a ceremony attended by executives of customer and partner companies with a presence in the Asian region, as well as Vetter and industry executives. Horiaki Suzuki, in his role as business development manager for Vetter Pharma’s group in Japan, K.K., will lead Vetter’s business activities in Japan, reporting to Chervee Ho based in Singapore in her role as director of key account management Asia Pacific.

The new office underlines the importance of Japan for Vetter’s business activities. As the second-largest single pharmaceutical market, Japan is home to a number of leading global companies that offer a promising injectable pipeline. It is also a point of departure for several established Japanese companies for increasing their global reach. As such, the new office will support customer relations and aid in the development of new business within Japan while strengthening the global position of Vetter, particularly in selected Asia Pacific markets. As a strategic partner, Vetter can build a world-wide clients through every phase of their drug product lifecycle, from early product development to launch to commercial supply.

“Our presence in Japan will help to increase awareness of Vetter’s services in this growing healthcare market by presenting our expertise and market position onsite,” noted Managing Director Peter Soelker. “Following the creation of our Asia Pacific hub in Singapore last year, the new office is a further development, establishing a dedicated presence in the most important single market of the region. This activity affords us the opportunity to strengthen personal contacts with national audiences.”

“Vetter’s decision to expand their presence in the Asia Pacific region and to open their first office in Japan is a strong message of their commitment to service the needs of this important market,” said Dr. Hitoshi Kuboniwa, senior vice president and general manager of Pharmaceutical Technology Division, Biopta. “As a trusted partner, we appreciate that step, wishing Vetter a company in general, and Ms. Ho and Mr. Suzuki in particular, a promising start for their onsite activities in Japan.”

The company was founded in 1959 by Helmut Vetter and originally called the Apotheker Vetter & Co. Arzneimittel GmbH Ravensburg. In 1958, Helmut Vetter opened a pharmaceutical production plant, the world’s first manufactur- ing in air- and water-tight packaging.

In 1965, his growing enterprise began operating as a contract manufacturer resource packaging dry and liquid drugs. Vetter founded its first foreign subsidiary in the United States in 1983 to handle U.S. and Canadian sales. The following year, the company was renamed Vetter Pharma Fertigung GmbH & Co. KG. In 1988, the U.S. Food and Drug Administration (FDA) granted Vetter’s Ravensburg facility approval to operate, which opened the U.S. market. Two years later, the company invested in a new culture media syringe, which remains a patented product.

In 1996, a second German production site was established, in Langenargen, and received approval to operate by the FDA two years later. In 2004, the company started construction on a second major site in Ravensburg. Completed at the end of 2006, the Ravensburg Vetter South production facility received permission by the regional board of West Germany.

At the same site, in 2009, Vetter opened a Japan office to bolster Asian inroads. For more information, visit www.DDN-News.com.
HAIFA, Israel—United Therapeutics Corp. has sent Pluristem Therapeutics Inc. a notice ending its licensing agreement for the development of PLX-PAD for the treatment of pulmonary arterial hypertension (PAH), Pluristem announced recently. Per the licensing agreement, Pluristem will regain full rights to PLX-PAD in PAH, in addition to all clinical data and regulatory submissions. Data from the Phase 1 trial conducted by United in September 2014 showed a good safety profile and an encouraging, if limited, efficacy trend.

“We thank United for the work they have completed on this project and believe PLX-PAD can make a significant contribution to the health of patients suffering from PAH. The data generated by United provides a good foundation to suggest that our cells can safely administered intra-nasally, with potential broad application, and can improve the quality of life for PAH patients,” remarked Zami Aberman, CEO and chairman of Pluristem.

Aberman, CEO and chairman of Pluristem.

### Hyped for HBV

**Johnson & Johnson acquires Novira Therapeutics and HBV portfolio in year-end deal**

**BY KELSEY KAUSTINEN**

NEW BRUNSWICK, N.J.—Johnson & Johnson is rounding out a busy year with the completion of its acquisition of privately held Novira Therapeutics Inc., a clinical-stage biopharmaceutical company developing therapies for the curative treatment of chronic hepatitis B virus (HBV) infection. With the completion of the deal, Novira is now part of the Infectious Diseases & Vaccines Therapeutic Area of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Johnson & Johnson and Novira first shared news of the deal on Nov. 4 with the announcement that the former would be acquiring 100 percent of Novira’s capital stock. No financial terms were disclosed.

“We are exploring several approaches in pursuit of a functional cure for this insidious disease. Bringing together NVR 3-778 with our own internal discoveries, we will leverage our vast experience in viral diseases to develop potentially transformational medicines for HBV patients,” Dr. William N. Hait, global head of Janssen Research & Development LLC, remarked in a press release.

This deal nets Johnson & Johnson Novira’s novel antivirals portfolio, which includes its lead candidate, NVR 3-778, a small-molecule, direct-acting antiviral that inhibits the HBV core or capsid protein. The compound is being evaluated for oral administration. The HBV core represents a novel, promising drug target with multiple activities required for viral replication and persistence, and inhibition of NOVIRA CONTINUED ON PAGE 24.

### AstraZeneca makes $575M deal for Takeda’s respiratory business

Deal, which is one several at year’s end, includes expansion of rights to roflumilast, the only approved oral PDE4 inhibitor for COPD

**BY KELSEY KAUSTINEN AND JEFFREY BOULEY**

LONDON—AstraZeneca has announced the establishment of a definitive agreement under which it will acquire Takeda Pharmaceutical Co. Ltd.’s core respiratory business. This deal includes an expansion of rights to roflumilast, which is marketed as Daxas in the United States and Daxas elsewhere, the only approved oral PDE4 inhibitor for the treatment of chronic obstructive pulmonary disease (COPD). AstraZeneca has been marketing the drug in the United States since the first quarter of the year, when it acquired the rights from Actavis. This agreement also net AstraZeneca access to several other marketed respiratory medicines and early pipeline products. Per the terms of the deal, AstraZeneca will pay Takeda $575 million for its respiratory business. In addition, roughly 200 staff will transfer to AstraZeneca once the transaction is complete. AstraZeneca expects the deal to close in the first quarter of 2016, and for it to be immediately accretive to earnings from 2016. Annual global sales for the three medicines included in this deal, excluding AstraZeneca sales of Daxas in the United States, totaled $1.8 billion for the period ending March 2015.

“The agreement with Takeda complements our respiratory business, one of our three main therapy areas, supports our return to growth and will be immediately accretive to earnings from 2016. Daxas in particular adds to our portfolio of treatments for patients with severe COPD,” Luke Miels, executive vice president of Global Portfolio and Product Strategy at AstraZeneca, said in a press release.

In addition to the Takeda deal, AstraZeneca, along with MedImmune, simultaneously announced a series of strategic initiatives in China. Among those initiatives is a strategic alliance with WuXi AppTec to produce innovative biologics locally in China. The agreement grants AstraZeneca the option to acquire WuXi AppTec’s biologics manufacturing capacity in Wuxi City in the next few years through an overall investment of roughly $100 million. Prior to that, WuXi AppTec will be AstraZeneca’s exclusive partner for R&D manufacturing for innovative biologics in China. DEALS CONTINUED ON PAGE 24.
A roundup of instrumentation, software and other tools and technology news

BY JEFFREY BOULEY

Our first roundup of the year for the hardware, software and materials that make life-sciences research and pharma/biotech R&D possible brings us an expansion in Singapore, the joining of a consortium for identification of treatment response predictors, a new interdisciplinary chemistry lab, the solving of an Ebola mystery, and insights into clinical trials and containment management security/compliance and a new path to accessing full-text journals.

Thermo Fisher opens new clinical services facility in Asia hub

SINGAPORE—Thermo Fisher Scientific recently announced the official opening of its new state-of-the-art CMF facility. Having established its first clinical services facility in Singapore in 2001, the move to this newly built facility will meet the growing demand for clinical supply services in the region. The new facility is equipped to handle and distribute ambient and cold chain supplies and returns management. Located on Toh Guan Road in Jurong East, the hub for Singapore’s biomedical and pharmaceutical companies, the new facility is nearly 70,000 square feet, which is more than 60 percent larger than the previous site and doubles the cold chain capacity.

The clinical services facility is also reportedly well-equipped with improved technologies and operational tools to serve a growing need for clinical supplies and trials in the region. This includes a larger storage system for its clinical supplies, a new climatic control energy consumption system that reduces the facility’s carbon footprint, and an overall building monitoring system that provides staff with timely updates on the facility’s conditions.

“Asia Pacific continues to be our fastest-growing market and a central contributor to our growth,” said Leon Wyszkowski, Thermo Fisher’s vice president of clinical services for North America and facility network. “For nearly 15 years, Singapore has been the central hub for our Asia-Pacific operations, due to its strategic location. With the opening of our larger and well-equipped facility, we aim to continue to build on our Singapore facility further and on the expertise of our local team, to strengthen our regional and global presence in the clinical supplies industry.”

Protagen AG joins MATURA Consortium

LONDON—Protagen AG, a company concerned with the development of advanced diagnostic tools to address some of the most severe autoimmune diseases, in early December announced that it will join the MATURA Consortium. The overarching mission of the MATURA Consortium is to improve patient care in Rheumatoid Arthritis (RA) by rationalizing therapy decisions through a stratified medicine approach.

MATURA (Maximizing Therapeutic Utilization for Rheumatoid Arthritis) aims to identify treatment response predictors which will allow the allocation of patients to subgroups defined by the therapy they are most likely to respond to, early in the disease process. RA provides the ideal setting for the introduction of a stratified medicine approach as the treatment is standardized, there is a significant non-responder rate to each marketed and commonly used drug, and early and effective therapy has consistently been shown to improve long-term outcomes, including joint damage, disability and employment.

Prof. Costantino Pitzalis from Queen Mary University of London, who leads the consortium, said: “We are delighted that Protagen has joined our consortium. There are currently a number of biologic treatments in RA and at the moment, we have no way of predicting favorable patient drug response before therapy selection and treatment.”

Adds Prof. Anne Barton from the University of Manchester, who co-leads the consortium: “Being able to accurately predict whether a treatment will work or not, would lead to more targeted initial treatment and, as well as greater efficacy and better quality of life for patients. Protagen and its unique, proprietary SeroTag platform is a new key asset group of established industry partners, and significantly support our quest for Treatment Response Predictors.”

“Our innovative SeroTag technology allows for the first time the systematic determination of response prediction markers to select the most appropriate drug and therapy for rheumatoid arthritis,” notes Stefan Müllner, Protagen’s CEO. “In addition, it enables new approaches for successful drug development, and to support patients, rheumatologists, payers and the pharma industry in our combined effort to improve patient management by rationalizing treatment decision. This is exactly what MATURA is aiming for and we feel privileged to be part of the consortium and support these efforts.”

Shimadzu teams with UWM to form interdisciplinary chemistry lab

COLUMBIA, Md.—Shimadzu Scientific Instruments recently announced the opening of the Shimadzu Laboratory for Advanced Applied and Analytical Chemistry at the University of Wisconsin-Milwaukee (UWM). The new 2,000-square-foot laboratory and office suite is a hub for research across the entire UWM campus, as well as a classroom for teaching the theory and practice of mass spectrometry. The new lab, located inside of UWM’s Kenwood Interdisciplinary Laboratory Complex, was made possible by a $1.13-million grant from Shimadzu Scientific Instruments.

Equipped with an array of Shimadzu’s analytical instruments, the lab is able to support diverse programs in drug discovery, pharmaceutical science, food and beverage, environmental science and other basic life-sciences and chemistry studies. The facility features six state-of-the-art mass spectrometers, sample preparation tools, UV-visible and FTIR spectrometers, liquid and gas chromatography systems and a fully equipped tissue culture suite to enable discovery and toxicology research.

The Milwaukee Institute for Drug Discovery (MIDD), part of UWM’s Department of Chemistry and Biochemistry, is the primary user of the lab. The institute uses the lab to conduct NIH-funded research on new drugs for pain, schizophrenia and asthma, as well as drug metabolism and stability and assessment of pharmacokinetics and biodistribution. Neuroscientists at the university have adopted the MALDI-TOF MS for studies on central nervous system development, pain processes and learning.

“Our relationship with Shimadzu allows us ready access to the market’s latest analytical innovations,” said Dr. Douglas Stafford, director of MIDD. “In the future, we hope that this lab will be used to host user workshops. The lab helps to keep our scientists ahead of the curve by staying connected to the wide network of MS users.”

The University of Wisconsin-Milwaukee, in conjunction with MIDD, is a vibrant, growing research community, supporting interdisciplinary applications in numerous scientific programs,” said Terry Adams, vice president of marketing at Shimadzu Scientific Instruments. “Shimadzu is proud to have our name associated with such an outstanding institution and we are eager to work with the many researchers and students utilizing this impressive laboratory.”

Illumina NGS helps solve Ebola mystery

SAN DIEGO—Next-generation sequencing (NGS) has helped researchers solve an Ebola mystery out of Liberia. The case, which was published in an issue of the New England Journal of Medicine late last year, provided molecular evidence of Ebola virus transmission between a man who had the Ebola virus and his female partner. The mystery: The man’s blood had tested free of Ebola 153 days prior to the transmission.

“The University of Wisconsin-Milwaukee, in conjunction with the MiSeq, was the only technique available that could provide a nearly complete full genome viral sequence from the semen sample that had barely detectable levels of Ebola when using qPCR. All they had to work with was this barely detectable virus level—probably 100- to 1,000-fold lower concentration than what they could even hope to get a genome using conventional methods. That’s where the RNA Access technology was critical to this project.”

The study findings have significant public health implications. The Centers for Disease Control and Prevention and the World Health Organization, for example, changed their recommendations for convalescent patients regarding sexual contact until more definitive information is obtained about how long the virus can remain in semen.

“The public health concern is: What’s going to be the long term effect of this concept of a ‘cleared Ebola infection’? This study has not
NOVIRA
Continued from Page 32
its function via NVR 3-778 has the potential to offer more efficient suppression of virus production and replication. NVR 3-778 has established a promising preclinical safety profile, and is currently being evaluated in a Phase 1 clinical trial in New Zealand. Novira’s pipeline also includes a second-generation core inhibitor with which is approaching preclinical development, and a ccr5DNA inhibitor, which is still in the discovery phase. As the company notes on its website, “When used in combination with the current standard of care (nucleosides and interferon), Novira’s core inhibitors are expected to provide greater and faster suppression of ccDNA and new virus production. Directly or indirectly, core inhibitors may also reduce HBV levels and release replicative intermediates, which is thought to enable therapy so that many CHB patients will no longer require lifelong treatment.”

This acquisition will enhance the ability of Novira’s research and development teams to continue to advance novel therapeutic candidates for chronic HBV infection,” said Christian S. Schade, CEO of Novira Therapeutics. “Novira is developing important new investigational curative treatments for HBV infection, and this acquisition is a great opportunity for the development of those assets to benefit from Johnson & Johnson’s resources, expertise and dedication to delivering innovative treatment options to the many patients with life-threatening infections.”

“Novira is developing important new investigational curative treatments for HBV infection, and this transaction is a great opportunity for the development of those assets to benefit from Johnson & Johnson’s resources, expertise and dedication to delivering innovative treatment options to the many patients with life-threatening infections.”

Given the lack of released financial details from the deal, it is unknown how much of a risk Johnson & Johnson might be taking in betting on Novira and an indication of the overall forecasted market growth compared to other therapeutic areas. The global hepatitis B market is forecast to reach roughly $5.5 billion by 2022 at a compound annual growth rate of 2.3 percent, according to a recent report by RnR Market Research. The Trefts team, a Forbes contributor, noted in a Nov. 10 article that “the overall market opportunity for Hepatitis B treatment is quite limited,” pointing out that diagnosis and treatment of the disease in adults are low, given that it is largely asymptomatic, and that “the current drugs are serving the market reasonably well, and there is threat from generic competition too.”

Still, the Johnson & Johnson group remains optimistic about the deal and the need within the hepatitis B market,” said Dr. Ken Blatt, global head of Infectious Diseases and Vaccines at Janssen and CEO of Ailois Biopharma, part of Johnson & Johnson, announcing the deal, pointing out in the original Nov. 4 press release that “approximately 60 percent of hepatocellular carcinoma is [sic] attributed to infection with the hepatitis B virus. With more than 350 million people worldwide, we seek to overcome treatment challenges, such as the requirement for people to endure lifelong therapy, through scientific innovation. Combining Novira’s recent breakthroughs with our vast experience in viral diseases, we endeavor to deliver novel medicines for patients suffering from this insidious disease.”

Better access to scientific data
IPSIFIC, Mass. — In early December, EBSCO Information Services (EBSCO) introduced a new information resource for researchers in the biotechnology and pharmaceutical industries. Biotechnology Source provides access to industry-leading, full-text journals from a single platform and is designed to help companies gain a competitive edge by providing fast access to relevant, current and accurate information. Biotechnology Source is said to have a very broad, customizable platform and content that includes more than 8,700 full-text journals, including many unique titles reportedly available only through this tool. In addition, current journal content is augmented by an extensive backfile.

Biotechnology Source is said to be easily integrated into a company’s workflow for increased visibility and utility, and it can conveniently be accessed via mobile devices. It provides increased discoverability to reliable information via top industry journals, helping ensure that researchers are returning search results of value to their organizations.

Joe Trager, senior director of product management, says Biotechnology Source helps researchers of all experience levels navigate an increasingly complex landscape of medical and pharmaceutical literature, while surfacing reliable information, noting: “Results-oriented organizational researchers and corporate librarians don’t have time for complex and laborious search engines. They want answers and information fast. Biotechnology Source gives researchers immedi-ately the information they need from the primary literature that has been care-fully vetted, so they know they can trust it to be reliable and relevant.”

EDGE
Continued from Page 32
only shows Ebola is detectable after long periods of time, but even with low viral loads—when it’s barely measurable—individuals can still carry someone,” says Schroth. “My group has been doing research into how to use the RNA Access method. Right now the kit we have is used to enrich for human genes, but we realized that the kit we have is used to enrich for resources, expertise and dedication benefit from Johnson & Johnson’s investment is a great opportunity for the development of next-generation biologics for both local needs and patients around the world.”

In other recent news of Astra Zeneca, the company confirmed in early December that it was exploring a deal with AstraZeneca announcing it had agreed to pay $4 billion to acquire a 55-percent stake in Acerta Pharma BV that would give it Acerta’s investigational drug acalabrutinib, which is being positioned as a rival to Ibruvica. The medicine has shown potential both in leukemia and auto-immune diseases. The news was followed by mid-December by an announcement that Acerta has hired an additional $2.5 billion and additional $2.5 billion before the end of 2018 or following FDA approval of acalabrutinib. AstraZeneca also has the option to purchase the remaining stake, up to $7 billion, contingent on the achievement of specific milestone related to the approval and marketing of acalabrutinib.

Mid-December also saw the completion of AstraZeneca’s purchase of ZS Pharma for $2.7 billion, a deal that enhances AstraZeneca’s hepatitis and cardiovascular disease product pipeline and gives it access to ZS Pharma’s potential hyperkalaemia drug, ZS-9 (sodium zirconium cyclosilicate).

In addition, around the same time, Regulus Therapeutics announced it had received a $10 million milestone payment by AstraZeneca for the clinical development of RG-125 (AZD4676), a GalNAc- conjugated anti-miR targeting microRNA-103/107 (miR-103/107) for the treatment of non-alcoholic steatohepatitis (NASH) in patients with diabetes/pre-diabetes. NASH is a serious condition that can cause scarring of the liver, and there is no approved treatment. RG-125 is the third microRNA therapeutic program in Regulus’ portfolio that has advanced into clinical development. RG-125 has shown effects on a pathway profile that mirrors that seen in people with NASH. Moreover, RG-125’s inhibition of miR-103/107 has been shown to lead to a sustained reduction in fasting glucose and fasting insulin levels.

EXOTAR’s Life Sciences Identity Hub now includes Veeva Vault
HERNDON, Va. — Exostar, whose cloud-based solutions help companies in life sciences, healthcare, aerospace and defense mitigate risk and solve their identity and access challenges, late last year announced a strategic agreement with Veeva Systems Inc., a leading provider of cloud-based solutions for the life sciences industry, Veeva Vault, a content management platform and suite of applications that reduces IT complexity and increases business agility, now can be accessed through Exostar’s Life Sciences Identity Hub. The connection enables life-sciences organizations and their partners to pre- pare, exchange, and store clinical trials documentation with the ease and security of a single credential. Exostar and Veeva are working together to streamline the provisioning process of creating Vault accounts with appropriate roles and permissions for all individuals participating in a clinical trial, regardless of their affiliation. Exostar’s Secure Access Manager (SAM) delivers an added layer of security when authenticating individuals. With SAM credentials, individuals enjoy a single sign-on experience to Vault and other applications connected to the Life Sciences Identity Hub. These credentials also support the inclusion of validated electronic signatures as documents are shared in Vault throughout clinical trials workflow processes.

“Bringing Vault and SAM together allows clinical trials personnel throughout our life-sciences community to fully benefit from the strengths of both solutions in an already integrated environment,” said Vijay Takanti, vice president of security and collaboration solutions at Exostar. “Vault enables global business processes and serves as a single source of truth for content, while SAM provides the access control and document signature security necessary for information protection and compliance.”

“Being part of the Exostar Life Sciences Identity Hub allows easy single sign-on for companies using Vault eTMF and the other Vault applications,” said Kathy King, executive vice president of Vault. “The seamless integration Exostar has created helps companies more effectively and securely work with multiple Vault applications across their partner or client ecosystem.”

The Exostar Life Sciences Identity Hub gives over 1,000 sponsors, CROs, investigators, academic institutions, application providers and other industry organizations a highly-secure, connect-once environment that reduces redundancy and expenditures while speeding integration and onboarding. More than 20,000 individuals productively collaborate with one another, accessing applications and data, as guided by access owners and controlled by SAM.

“The value Exostar and Veeva together are delivering perfectly illustrates the whole being greater than the sum of the parts,” said Daniel Pfeifle, Exostar’s Vice President of Sales and Marketing. “Now that Vault is connected to the Life Sciences Identity Hub, we look forward to replicating this value throughout the industry.”
“Each year, CDER approves hundreds of new medications, most of which are variations of previously existing products, such as important new dosage forms of already approved products, or cost-saving generic formulations,” noted Dr. Janet Woodcock, director of CDER. “These new products contribute to quality of care, greater access to medication, more consumer choice, and a competitive marketplace that enhances affordability and public health. However, products in a small subset of these new approvals, that we refer to as novel new drugs, are among the more truly innovative products that often help advance clinical care to another level.”

The novel new drugs approved by CDER in 2015 were Addyi, Alecen, Aricep, Arixtra, Bridion, Cholbham, Corlanor, Csernty, Cotellic, Cresembra, Daktinna, Darzalese, Empipli, Entresto, Faryjak, Genvoyya, Ilranc, Kanuma, Kengreal, Kybella, Leniviva, Omur, Natpara, Ninalor, Nucala, Odimoz, Orkambi, Portrazza, Praluent, Praxbind, Relpabha, Resumbi, Savaya, Sanius, Tagrisso, Tresiba, Unituxin, Uptravi, Varub, Veltassa, Viberzi, Vyzlayz, Xuriden, Yondelis and Zarampik.

Looking specifically once more to the rare disease category, some of the notable new drugs highlighted by CDER in its report on 2015 approval were Kanuma to treat lysosomal acid lipase deficiency; Orkambi for the lung disease cystic fibrosis; Strensiq, a long-term enzyme replacement therapy in patients with infantile- and juvenile-onset hypophosphatasia, a serious and sometimes fatal bone disease; Unituxin to treat pediatric patients with high-risk neuroblastoma; and Xuriden to treat patients with hereditary orotic acidduria, a condition that can result in blood abnormalities (anemia, decreased white blood cell count, decreased neutrophil count), urinary tract obstruction, failure to thrive and developmental delays.

As always, compromises were not made in our review standards. We considered the applications as efficiently as possible,” Jenkins asserted. “In short, each of these therapies had to demonstrate that it was safe and effective before being approved. I am pleased and proud to be part of a team that helped bring these new drugs to market as safely as possible.”
Clinical Data Review solution leverages TIBCO Spotfire to optimize clinical data analysis

PerkinElmer

The Clinical Data Review offering is built on TIBCO Spotfire, which provides an enterprise-class analytics platform featuring easy data integration, role-based authorization and automation services. It offers medical monitors, safety review teams, biostatisticians, data managers, pharmacologists and others who analyze clinical data a powerful and advanced analytics solution for overcoming data review challenges. The solution enhances clinical data management and medical review workflows, allowing organizations to make more informed decisions on the safety and efficacy of therapeutics earlier in their development. Customers can fundamentally improve processes by identifying protocol violations and dropouts early, along with early safety signal detection. Population, subpopulation and patient-level data is brought together and reviewed at the presentation layer. Contextual collaboration enables clinicians and data management to quickly identify data quality issues and perform adaptive monitoring.

For more information, visit www.ddn-news.com
RNA therapies aimed at solving cardiometabolic and lipid disorders

BY LLOYD DUNLAP

S THOMAS Edison said (apparently in various ways on more than one occasion), “Genius is 1 percent inspiration, 99 percent perspiration.” With a tagline of “Innovate. Welcome to Akcea,” on its website home page, it’s clear that relative newcomer Akcea Therapeutics has the inspiration to go with the “quitter” line on that same page describing itself as “A company committed to transforming cardiometabolic lipid disorders.” That quitter sentence, of course, is where the perspiration comes in, and it’s a sentence that Paula Soteropoulos is here to tell us about.

DDNews: Please tell our readers about Akcea Therapeutics, how it originated and its experience to date.

Soteropoulos: Akcea Therapeutics was established in January 2015 to develop and commercialize new treatments for serious cardiometabolic diseases. The company has clinical trials for therapies in development across the range from preclinical through Phase 3 programs. All of these are advanced RNA-targeted antisense therapies designed to address rare lipid disorders and more prevalent serious cardiometabolic diseases with significant unmet medical need.

Akcea Therapeutics is a wholly owned subsidiary of Ionis Pharmaceuticals Inc., a leader in RNA-targeted therapeutics. Akcea’s portfolio, based on the antisense technology platform developed at Ionis, is focused on development and commercialization of therapies with the potential to transform the treatment of serious cardiometabolic diseases.

2015 was an exciting year for us. Our lead drug, volanesorsen, which prevents the formation of the protein Apo C-III, reached two important milestones: we closed enrollment in our pivotal study in patients with familial chylomicronemia syndrome (FCS), and we initiated our Phase 3 study in patients with familial partial lipodystrophy (FPL). Results from the Phase 2 program for volanesorsen were reported in two separate publications in the New England Journal of Medicine. We also had several announcements related to the progress of our antisense program targeting extreme levels of Lp(a), an independent, genetic contributor to aggressive, premature heart disease, including a report on a clinical study that was published in The Lancet.

DDNews: What encouraged you to join the company as CEO?

Soteropoulos: I have a wonderful history with the Ionis team from my days working in collaboration with them while at a previous company. When they reached out to me about an opportunity to start a new company based on these very important medicines, it was a no-brainer. At the time I was working at a preclinical-stage start-up company and I realized that my passion was working on drug programs that were closer to patients. I found that I really missed the late-stage development and commercialization aspects of drug development. With Akcea and the resources and capabilities from Ionis, we can focus on building a world-class team to advance medicines that can transform patients’ lives. Akcea is a start-up, but with the advantage of being able to hit the ground running with an existing pipeline of late-stage drugs and also the depth of an early-stage clinical pipeline. To be involved in a startup with the potential represents a unique experience with many compelling opportunities to make a positive difference.

DDNews: How does RNA targeting work to treat cardiovascular disease and lipid disorders?

Soteropoulos: There are underserved cardiometabolic diseases that, despite significant research progress over the years, remain limited or no treatment options. For both rare cardiometabolic diseases and others that affect broader patient populations, we desperately need new approaches to treat these conditions. While traditional drugs modify proteins associated with diseases, antisense drugs are designed to prevent the formation of these proteins in the first place. They mirror a specific sequence in the RNA that codes for a particular protein. This precise match-up of drug to target RNA is what makes antisense drugs highly specific. And because antisense drugs target RNA instead of proteins, they are able to reach disease targets that often cannot be addressed through other drug technologies.

One advantage of using antisense drugs to target lipid disorders and cardiovascular disease is due to the fact that, while anti-sense drugs can distribute to a wide variety of tissues, they accumulate especially well in the liver. This is advantageous because a number of proteins associated with cardiovascular and lipid disorders are produced in the liver and can be effectively targeted with antisense drugs.

DDNews: Is ISIS 304801 your most advanced clinical program and which other targets are you working on?

Soteropoulos: Our lead product candidate, volanesorsen (formerly known as ISIS-APOCIIIRx or ISIS 304801), is in Phase 3 studies for the treatment of two rare and severe lipid disorders: FCS and FPL. Volanesorsen prevents the formation of the protein Apo-C-III, a key regulator of triglyceride levels in the blood. Reducing Apo-C-III levels has been shown to lower triglyceride levels. FCS is a rare genetic disorder that is also known as Fredrickson type 1 hyperlipoproteinemia or familial lipoprotein lipase deficiency. Patients with FCS are unable to effectively cleave lipoprotein particles containing triglycerides, resulting in the formation of potentially life-threatening pancreatitis. FPL is a rare metabolic disorder characterized by abnormally high fat distribution across the body. Patients with FPL are unable to store fat in normal fat stores, whereas excess triglycerides are stored in the liver and muscle, and accumulate at high levels in the bloodstream, which increases the risk of pancreatitis, hepatic steatosis and NASH, enlarged livers, polygenic ovarian syndrome and premature cardiovascular and liver disease. Patients with FPL also often have severe insulin resistance and, in affected women, display features of hyperandrogenism.

Results from two Phase 2 studies of volanesorsen were published in two separate articles in the New England Journal of Medicine. Phase 2 results in patients with FCS were reported in December 2014 and Phase 2 results in patients with less severe forms of hypertriglyceridemia were published in July 2015. In both studies, patients treated with volanesorsen showed an approximately 70 percent reduction in triglycerides. In FCS patients, Apo-C-III levels were reduced up to 90 percent, triglyceride levels were reduced approximately 90 percent and all patients showed a 90 percent reduction in triglyceride levels below 500 mg/dL, a level that is recognized to be below the level associated with elevated risk of pancreatitis. Results in FCS patients also indicate the potential existence of additional complemen-
tary pathways for triglyceride clearance that were not previously well characterized. We have completed enrollment for our Phase 3 pivotal trial study for patients with FCS, and we very much look forward to seeing what we learn from the results from this study and our FPL Phase 3 study.

DDNews: How do antisense therapies differ from others?

Soteropoulos: Antisense drugs, also often referred to as antisense oligonucleotides (ASOs), are short synthetic analogs of DNA or RNA that bind to a specific target within the cell to trigger a targeted degradation of the messenger RNA (mRNA) by Watson-Crick hybridization. Antisense drugs differ from small molecules and antibodies in several key ways.

First, antisense drugs are designed to address a specific target after binding to the target RNA. They can then work via one of several different mechanisms. Depending on how the drug was designed, antisense drugs can either increase or decrease the production of the specific protein coded for by the target RNA. They can also work to degrade toxic RNAs.

Second, antisense drugs are large- to medium-sized pharmaceutical molecules. Compared with small- molecule drugs such as aspirin or biologics such as insulin, the relatively large size, negative charge and high protein binding and high serum protein binding of ASOs make them impermeable to the blood-brain and placental barriers. Because antisense drugs are water-soluble and bind with low affinity but high capacity to serum proteins, they distribute well to tissues throughout the body without the need for special formulations.

Lastly, ASOs are metabolized by endo-
nucleases and do not interact with CFTR pathways. Reflecting these attributes, there are no known drug-drug interactions associated with antisense drugs in general. This is important because patients with complex cardiometabolic disorders such as FCS and FPL may take multiple medications due to concomitantly prescribed therapies.

DDNews: When do you anticipate your first regulatory review of an Akcea therapy?

Soteropoulos: The data from our Phase 3 pivotal trial in FCS will be available in the first half of 2017. We are positioned to file for approval and, pending regulatory approval, advance rapidly to commercialization in the U.S., Europe and other global markets.

We feel very privileged to be actively engaged in bringing these promising therapies forward with the potential to significantly improve quality of care in patients with serious cardiometabolic diseases.

Q&A: Paula Soteropoulos of Akcea Therapeutics

Paula Soteropoulos joined Akcea as president and CEO upon its formation in January 2015. Prior to joining Akcea, she was a member of the executive leadership team of Moderna Therapeutics as the Cardiometabolic Business Unit general manager and senior vice president of strategic alliances. Prior to Moderna, Soteropoulos spent 21 years at Genzyme Corp., where she was instrumental in advancing new products from discovery through clinical development and commercialization, with significant roles driving strategy, sales and marketing, and business development. Additionally, Paula led manufacturing process development, strategic capacity planning and supply chain development.

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CRISPR treats genetic disorder in adult mammal

DURHAM, N.C.—Researchers have used clustered regularly interspaced short palindromic repeats (CRISPR) technology to treat an adult mouse model of Duchenne muscular dystrophy. This reportedly marks the first time that CRISPR has successfully treated a genetic disease inside a fully developed living mammal with, as the researchers put it, “a strategy that has the potential to be translated to human therapy.”

The researchers from Duke University, whose paper appears in the Dec. 30 issue of Science, had previ-ously used CRISPR to correct genet-ic mutations in cultured cells from Duchenne patients, and other labs had corrected genes in single-cell embryos in a laboratory environment. But the latter approach is currently unethical to attempt in humans, the university notes, and the former faces many obstacles in delivering treated cells back to muscle tissues.

Another approach, which involves taking CRISPR directly to the affected tissues through gene therapy techniques, also faces chal-lenges, particularly with delivery. In the new study, Duke University researchers overcame several of these obstacles by using a non-pathogenic carrier called adeno-associated virus (AAV) to deliver the gene-editing system.

“Recent discussion about using CRISPR to correct genetic muta-tions in human embryos has right-fullly generated considerable con-cern regarding the ethical impli-cations of such an approach,” said Charles A. Gersbach, an associate professor of biomedical engineer-ing at Duke University. “But using CRISPR to correct genetic muta-tions in the affected tissues of sick patients is not under debate. These studies show a path where that’s possible, but there’s still a consid-erable amount of work to do.”

Duchenne muscular dystrophy is caused by problems with the body’s ability to produce dystrophin, a long protein chain that binds the interior of a muscle fiber to its surrounding support structure. Dystrophin is coded by a gene containing 79 pro-tein-coding regions, called exons. If any one exon gets a deleterious mutation, the chain does not get built. Without dystrophin provid-ing support, muscle tends to shred and slowly deteriorate.

Duchenne affects one in 3,500 newborn males. Most patients are wheelchair-bound by age 10 and don’t live beyond their 20s or early 30s. The mutation is on the X chromo-some so female children with two X chromosomes should have at least one functioning copy of the gene.

Gersbach has been working on potential genetic treatments for Duchenne with various gene-alter-ing systems since starting his lab at Duke in 2009. His lab recently began focusing on CRISPR/Cas9, a modified version of a bacterial defense system that targets and slices apart the DNA of familiar invading viruses.

While Gersbach has had success in cultured patient cells by using a jolt of electricity to punch holes in their membranes to deliver the CRISPR system, this strategy was not practical in a patient’s muscle tissues.

“A major hurdle for gene editing is delivery,” Gersbach said. “We know what genes need to be fixed for certain diseases, but getting the gene editing tools where they need to go is a huge challenge,” said Chris Nelson, the fellow in Gersbach’s laboratory who led the work. “The best way we have to do it right now is to take advantage of viruses, because they have spent billions of years evolving to figure out how to get their own viral genes into cells.”

Nelson and Gersbach began working on packaging gene edit-ing tools into AAV. AAV is in use in many late-stage clinical trials in the United States, and has already been approved for use in one gene therapy drug in the European Union. There are also different versions of AAV that can preferentially go to different tissues, such as skeletal and cardiac muscle, so researchers can deliver them to the muscle tissue.

But there’s always a catch, the university noted of the research, and for Gersbach it was a matter of size. “AAV is a really small virus and CRISPR is relatively large,” said Gersbach. “It simply doesn’t fit well, so we still had a packaging problem.”

The solution came from Feng Zhang, an investigator at the Broad Institute of the Massachusetts Insti-tute of Technology and Harvard. Earlier this year, Zhang described a CRISPR system from a different bac-terium than the one commonly used. In the natural bacterial immune system, CRISPR CONTINUED ON PAGE 39

Shire zeroing in on Baxalta?

Shire Plc (pictured here) has its sights set on buying Baxalta for more than $30 billion.

Dublin—With media outlets cit-ing unnamed people close to the matter, Bloomberg has first bro-ken the news, the first days of the new year brought news that Shire Plc was nearing a deal to acquire U.S. biotech competitor Baxalta Inc., based in Bannockburn, Ill. The news sent Baxalta shares up more than 10 percent in premarket trading, while Shire dipped slightly by a little over 1 percent.

As of the writing of this article, the scuttlebutt was that the two companies could announce a deal possibly on or before Jan. 11. The price was rumored to be about $32 billion in cash and stock, not counting debt. That’s in line with an unsolicited offer of $30 billion by Shire during sum-mer 2015—which Baxalta initially rejected—and considerably higher than the $5.9 billion Shire paid for biotech Dyax Inc. in November.

Should the deal go through, the combined company could generate $20 billion in sales by 2020 and boast as many as 30 new drugs for launch over five years.
Merus and Institut Gustave Roussy team up to develop innovative bispecific antibodies

UTRECHT, The Netherlands & VILLEJUIF, France—Jan. 4 saw Merus B.V., a clinical-stage immuno-oncology company, and Institut Gustave Roussy, a leading comprehensive cancer center in Europe, announce that they had entered into a strategic collaboration to jointly develop bispecific antibodies for therapeutic immuno-oncology applications.

Under the terms of the agreement, Merus and Gustave Roussy will collaborate on the design and conduct of basic, preclinical and translational research studies and early clinical studies leveraging Merus’ portfolio of therapeutic human bispecific antibody candidates, including bispecific antibody candidates that are designed to recruit and activate T cells for the treatment of patients with acute myeloid leukemia.

“Gustave Roussy is an internationally renowned leader in cancer research, and we look forward to working with them to conduct early clinical trials and conduct preclinical research to further develop our understanding of how a patient’s immune system can be activated to eliminate cancer cells,” said Dr. Ton Logtenberg, CEO of Merus. “Gustave Roussy’s outstanding preclinical and clinical oncology teams, coupled with Merus’ bispecific antibody pipeline, create a powerful research platform capable of identifying important advancements in the area of immuno-oncology.”

Merus’ bispecific antibody therapeutics, Biclonics, are based on the full-length IgG format and have been observed in preclinical studies to have several of the same features of conventional monoclonal antibodies, such as long half-life and low immunogenicity.

CRISPR CONTINUED FROM PAGE 38
system, CRISPR is the mug shot that helps identify the target DNA, and Cas9 is the blade that slices the strands. The large Cas9 protein typically used by researchers comes from the bacterial species Streptococcus pyogenes. After scouring the bacterial kingdom, Zhang discovered the much smaller Cas9 protein of Staphylococcus aureus, which was small enough to fit comfortably inside of AAV.

In the study, researchers worked with a mouse model that has a debilitating mutation on one of the exons of the dystrophin gene. They programmed the new CRISPR/Cas9 system to snip out the dysfunctional exon, leaving the body’s natural repair system to stitch the remaining gene back together to create a shortened, but functional, version of the gene.

Besides being much easier and more efficient than replacing the dysfunctional exon with a working copy, simply nipping out the weak link is a strategy that would be effective in a larger swath of the patient population, according to the researchers.

Gersbach and his team first delivered the therapy directly to a leg muscle in an adult mouse, resulting in the restoration of functional dystrophin and an increase in muscle strength. They then injected the CRISPR/AAV combination into a mouse’s bloodstream to reach every muscle. The results showed some correction of muscles throughout the body, including in the heart—a major victory because heart failure is often the cause of death for Duchenne patients.

“These results coming from our first experiments are very exciting. From here, we’ll be optimizing the delivery system, evaluating the approach in more severe models of DMD and assessing efficiency and safety in larger animals with the eventual goal of getting into clinical trials,” said Gersbach.

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* Based on PubMed data, October 2015.