Meet the Mini-Brain
Axosim licenses revolutionary Mini-Brain technology from Johns Hopkins

BY MEL J. YEATES
NEW ORLEANS—Axosim Inc. recently announced an exclusive license from Johns Hopkins University to intellectual property underlying the “Mini-Brain” technology, which uses induced pluripotent stem cells (iPSCs) to create functional models of the human brain. The technology enables researchers to study key brain functions, test new therapies and screen for toxic substances at an early stage of research in human rather than animal models.

“Acquiring rights to the intellectual property underlying the Mini-Brain technology is a major step forward in our drive to transform neurology drug research,” says Dr. Lowry Curley, CEO of Axosim. “The Mini-Brain technology complements our innovative Nerve-on-a-Chip platform and accelerates our strategy of providing the broadest and most scientifically robust neuroscience models to our growing roster of biopharmaceutical partners.”

The Mini-Brain technology is one of the key opinion leaders in the field of microphysiological systems. His Mini-Brain technology is the most reliable and advanced platform to recapitulate the human central nervous system,” Curley adds. “An important link between the Nerve-on-a-Chip and Mini-Brains is that each was the first ever to show mature myelination in a microphysiological model of the peripheral and central human nervous systems, respectively, a critical feature for the study of neurological diseases. The scientific potential of building on this link was so apparent that when members of our senior teams first met at a major scientific meeting, there was immediate interest in working together.”

Almost 90 percent of drugs that look promising in animal models fail in humans, driving up the average cost and time to translate into clinical trials—but with kidney disease, they often don’t know it. So we have to really develop a forum that they want to engage in so they can learn about their disease and participate in research too. We think it’s going to help people become more educated about kidney disease, says Dr. Lesley Inker, chair of the NKF Patient Network Steering Committee, associate professor of Medicine at Tufts University School of Medicine and director of the NKF Patient Network.

GSK, University of California

To establish new lab for genetic and CRISPR research

BY KELSEY KAUSTINEN
LONDON & SAN FRANCISCO—Under the auspices of a five-year collaboration, GlaxoSmithKline (GSK) and the University of California (UC) will establish the Laboratory for Genomics Research (LGR), a state-of-the-art lab dedicated to investigating how gene mutations cause disease and developing new technologies with CRISPR to advance drug discovery.

The idea for the LGR comes from Prof. Jennifer Doudna, University of California, Berkeley, a co-inventor of CRISPR technology and Howard Hughes Medical Institute (HHMI) Investigator; who led the team that developed the Mini-Brain technology, is one of the key opinion leaders in the field of microphysiological systems. His Mini-Brain technology is the most reliable and advanced platform to recapitulate the human central nervous system,” Curley adds. “An important link between the Nerve-on-a-Chip and Mini-Brains is that each was the first ever to show mature myelination in a microphysiological model of the peripheral and central human nervous systems, respectively, a critical feature for the study of neurological diseases. The scientific potential of building on this link was so apparent that when members of our senior teams first met at a major scientific meeting, there was immediate interest in working together.”

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A NEW NETWORK

National Kidney Foundation introduces its plan for an expansive kidney disease registry

BY KELSEY KAUSTINEN
NEW YORK—In the case of diseases without immediately obvious symptoms, patients may not even know of their disease state. Kidney disease is one such “silent disease,” and the National Kidney Foundation (NKF) has laid out its plan for establishing a national registry for patients to combat the issue: the NKF Patient Network, an interactive platform that links patient-provided data on health history and preferences with clinical and laboratory data. According to the NKF, this approach “will enable individualized educational resources, research, clinical care and health policy decisions to be centered on the patient.”

“Contrasting with, say, migraine sufferers or people with asthma—patients know they have diseases, they want a way to learn about their condition and to talk to other people and potentially participate in clinical trials—but with kidney disease, they often don’t know it. So we have to really develop a forum that they want to engage in so they
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WHO might be overestimating cancer treatment prices, potentially stifling R&D

SAN FRANCISCO—The World Health Organization (WHO) is advocating that cancer treatment prices are excessive, but its report justifying this conclusion contains significant biases that drastically overestimate the revenues multiple over research and development costs, according to a new issue brief released in June by the Center for Medical Economics and Innovation at the non-partisan Pacific Research Institute (PRI).

“Cancer medications have revolutionized treatment, and it’s unfortunate if the WHO’s flawed analysis jeopardizes patients’ access to these life-saving medicines,” says author Dr. Wayne Winegarden, who is director of the Center for Medical Economics and Innovation at PRI and a PRI senior fellow in Business and Economics, as well as the principal of Capitol Economic Advisors. “The misinformation perpetuated by the study inappropriately supports the imposition of price controls and more government regulation, which would actually threaten innovation and make cutting-edge cancer treatments less available to patients.”

In the issue brief, titled “A Review of the WHO Technical Report,” Winegarden analyzes an oft-cited study by the WHO (“Pricing of Cancer Medications and its Impacts”), which concludes that life-sciences companies receive an average return of $14.50 for every dollar invested in R&D.

Winegarden notes that the report is flawed in two key areas. First, he maintains, it did not include 37 percent of the FDA-approved cancer medications in its study; thus, in his opinion, the WHO study significantly underestimated R&D costs and overstated the revenue multiple of sales revenues to R&D expenditures.

Additionally, the WHO study does not account for the time value of money, according to Winegarden. By taking into account these factors, Winegarden estimated that the multiple of sales revenue to R&D could be inflated by 63.4 percent for the 99 drugs studied, and by 76.7 percent for all 156 drugs approved by the FDA over this time period.

Accounting for the first bias—incorporating all 156 approved cancer medications—would reduce the revenue multiple to $5.20 in revenue per dollar invested in R&D; in addition, accounting for the time value of money could reduce the figure to $3.16 per dollar invested, according to Winegarden.

“By applying basic economic principles, our brief concludes that the estimates of returns on R&D for cancer treatments could be inflated by as much as 350 percent or more in the WHO study,” Winegarden said. “When it comes to matters of life and death, it’s important that studies like these take an honest look at the issue, one that doesn’t pave the way for troubling policy changes that would worsen the problem.”

Lack of reimbursement could limit impact of digital therapeutics

LONDON—A major barrier to the widespread use of digital therapeutics (DTx) is the limitation or lack of reimbursement by public and private health insurance providers, says data and analytics company GlobalData. According to the firm, DTx have been defined by the Digital Therapeutics Alliance as “delivering evidence-based therapeutic interventions to patients that are driven by high-quality software programs to prevent, manage or treat a medical disorder or disease. They are used independently or with medication, devices or other therapies to optimize patient care and health outcomes.”

And, as noted by Alessio Brunello, a pharma analyst at GlobalData, “Due to increasing levels in healthcare spending combined with declining R&D returns, DTx represents a new way of treatment for pharma companies, in which regulatory approved digital systems are used to treat medical conditions as prescribed therapeutic interventions.”

Further, GlobalData’s report “Digital Therapeutics and Their Impact on Healthcare” maintains that there is an unmet need for patient-centered care and DTx implementation is designed to fill that need to deliver reliable, evidenced-based interventions with a high control of the quality of personalized care based on individual patients’ needs. Moreover, says GlobalData, DTx have the opportunity to speed up clinical trials and create a more fit for purpose approach through improved recruitment and retention of patients.

Continued Brunello: “The industry’s interest in value-based care and patient centricity is helping drive the adoption of DTx, as insurers and payers can use data and analytics to manage healthcare costs and help patients to receive appropriate treatment. This will drive the adoption of DTx as healthcare stakeholders are placing increasing emphasis on cost-effectiveness.”

DTx can be used to prevent, manage or treat diseases across diverse indications, particularly chronic conditions, such as diabetes, respiratory diseases and mental health conditions/neurological disorders. They are prescribed as monotherapy (standalone) or together with other therapies (adjunctive or add-on) or devices to optimize health outcomes.

Yet, as Brunello concluded, “Despite DTx technologies potentially reducing total healthcare costs, increasing trial efficacy and improving patients’ health, there are a few challenges to address before they become an integral part of modern medicine, such as better alignment between providers, pharmaceutical companies and payers.”

Biopharma dealmaking will rise

PHILADELPHIA—The 11th annual “Dealmakers’ Intentions Study” from Syneos Health Consulting, a biopharmaceutical management consulting firm, indicates that there will be an acceleration in dealmaking across all deal types. The 2019 survey results indicate that buyers appear more willing to accept risk associated with opportunities in the early development and rare disease categories.

The study, released during a Super Session at the BIO International Convention in Philadelphia, provides a review of biopharmaceutical dealmakers’ intentions around licensing and acquisitions going out about 12 months from the middle of this year, identifying areas of greatest opportunities for buyers and sellers. For the first time, the study also includes new data on buyer and seller interest in rare disease opportunities.

“In this healthy dealmaking environment, buyers are intensely focused on finding assets that are the best strategic fit for their business and are being heavily influenced by the probability of regulatory and technical success,” said Neel Patel, senior managing director of the Commercial Advisory Group at Syneos Health Consulting. “Sellers can take advantage of these expanding dealmaking options by clearly understanding and communicating their commercial value and using creative dealmaking options to avoid financial disagreements.”

Key findings of the report include:

• M&A landscape continues bullish run with potential to reach $200B to $250B in 2019
• Despite a steep market decline in the last quarter of 2018 and a government shutdown, 2019 is projected to be one of the strongest years for dealmaking in the past decade, paralleling the mega-mergers of 2009 and growth achieved during 2014 and 2015.
• Buyers are more optimistic than sellers that there will be an acceleration in dealmaking across all deal types, suggesting buyers are more likely to pursue opportunities and sellers are more likely to consider opportunities.
• Despite a decline in the number of deals going forward, total deal value continues to grow, particularly in oncology and rare disease categories.
• While 2019 is expected to be a strong year for dealmaking, the number of deals is projected to be lower than recent years.”
MARKET NEWS

MARKET INDICES

Pharmaceutical Index

Biotechnology Index

A RUN OF THE FINANCING ROUNDS

LEADING OFF our latest roundup of financing rounds in pharma and biotech is news from San Francisco-based Concentric Analgesics Inc.—a clinical-stage biopharmaceutical company focused on developing and commercializing novel, non-opioid pain therapeutics—that it recently completed a $76-million Series B financing. Concentric intends to use the proceeds from the financing to advance its lead product candidate, CA-008, into late-stage clinical trials targeting the post-surgical market. CA-008, a non-opioid therapeutic reportedly providing long-lasting pain relief after a single local administration, has previously received both Breakthrough Therapy Designation and Fast-Track Designation from the U.S. Food and Drug Administration (FDA). Proceeds will also be used to further develop the company’s pipeline of product candidates for chronic refractory pain and osteoarthritis.

“This financing is a significant milestone that will enable us to continue to rapidly advance CA-008 into late-stage clinical development,” said Dr. Frank Bellizzi, CEO of Concentric Analgesics. “We are especially gratified to have such strong support from top-tier healthcare investors who share our vision and determination to address the critical unmet need for truly long-lasting, non-opioid pain therapies.”

Unlike local anesthetics, CA-008 is designed to selectively desensitize pain-conducting nerve fibers without producing numbness or weakness. CA-008, injected during surgery, has the potential to reduce—and in some patients, eliminate—the need for opioids in the post-surgical recovery period. The compound is designed to provide clinically meaningful pain relief for a week or more resulting in quicker return to normal activities.

Ayala raises $30M in Series B

REHOVOT, Israel & WILMINGTON, Del.— For its part, Ayala Pharmaceuticals Inc., a clinical-stage company developing medicines for cancers that are genetically defined, recently announced the successful completion of a $30-million Series B financing that will fuel the company’s plans to advance the clinical development of lead product candidate AL101, a pan-Notch inhibitor that is currently being evaluated for adenoid cystic carcinoma (ACC). The company intends to advance the Phase 2 study in ACC and initiate a Phase 2 clinical trial in triple negative breast cancer (TNBC).

“The strategic investment by Novartis and others will enable us to rapidly advance our lead product candidate AL101 into clinical development in multiple systems,” said Dr. Roni Mamluk, CEO of Ayala. “With this funding, we are well positioned to complete the ongoing Phase 2 study of AL101 in ACC and begin a Phase 2 study with AL101 as a targeted therapy for patients living with TNBC bearing Notch activating mutations/fusions.”

The FDA recently granted Orphan Drug Designation to AL101 for the potential treatment of ACC.

MODAG launches out of stealth mode with Series A

WENDELHEIM, Germany—In late June, MODAG announced the completion of a €12-million (about $13.6 million) Series A financing round, launching out of stealth mode to advance lead candidate anle138b into clinical development in multiple systems—Parkinson’s disease, Alzheimer’s disease, and other neurodegenerative diseases. Anle138b is in Phase 2 clinical development in multiple systems and is positioned to advance leading candidate anle138b into clinical development in multiple systems—Parkinson’s disease, Alzheimer’s disease, and other neurodegenerative diseases. Anle138b aims to halt the progression of Parkinson’s disease, an atypical form of Parkinson’s disease. The company was founded in 2013 based on research conducted by Dr. Giese (Ludwig Maximilian University of Munich) and Dr. Griesinger (Max-Planck-Institute for Biophysical Chemistry) examining protein aggregation and its toxic properties in neurodegenerative diseases to develop therapeutic options for conditions without available disease-modifying treatments.

The financing round was led by Massa Investment AG and will support the corporate growth as well as the clinical development of anle138b, which has already demonstrated the potential to halt MSA progression in preclinical studies. Jeff Putman of Massa Investment AG will join MODAG’s board.

TreeFrog raises over €7M six months after incorporation

BORDEAUX, France—May saw TreeFrog Therapeutics, a stem cell company, announce that it had raised €7.1 million (approximately $7.8 million) in a Series A funding round. The proceeds will be used to transition the company’s C Stem technology to cGMP standards by 2021 and to develop proprietary and collaborative cell therapy research programs in a wide array of indications—Huntington’s disease, Parkinson’s disease, heart failure, diabetes and NASH, among others—with the objective of a first-in-human clinical trial in 2024.

TreeFrog Therapeutics was incorporated in November 2018. The company recently announced that it had delivered the first batch of 143 million human induced pluripotent stem cells to Imagine Institute. These cells reportedly were amplified in only seven days without compromising on quality, an amplification factor said to be about 30 times higher than current industry standards.
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Gilead, Goldfinch take aim at kidney disease

All told, the total deal value could reach over $2B if all milestones are met

BY KELSEY KAUSTINEN

FOSTER CITY, Calif. & CAMBRIDGE, Mass.—In its first deal for the year—and its largest by price since the company was established—Goldfinch Bio Inc. has announced a collaboration with Gilead Sciences Inc. for the discovery, development and commercialization of a pipeline of therapeutics for diabetic kidney disease (DKD) and select orphan kidney diseases.

Per the agreement, Gilead will pay Goldfinch $35 million up front, which includes a $5 million investment, as well as $54 million to support the development of the Kidney Genome Atlas (KGA) platform for diabetic kidney disease. Goldfinch also stands to receive up to $1.35 billion in additional payments for the first five collaboration programs if certain milestones are met, as well as tiered royalties on sales of products.

Goldfinch Bio and Gilead Sciences will collaborate on a pipeline of therapeutics for diabetic kidney disease and select orphan kidney diseases.

A better picture of how antibiotics kill

Machine learning reveals metabolic pathways disrupted by the drugs

BY DONNEWS STAFF

CAMBRIDGE, Mass.—Most antibiotics work by interfering with critical functions such as DNA replication or construction of the bacterial cell wall, but as it turns out, these mechanisms represent only part of the picture of how antibiotics act. Massachusetts Institute of Technology (MIT) researchers developed a new machine-learning approach to discover an additional mechanism that helps some antibiotics kill bacteria, noting in a new paper about their study of antibiotic action that this secondary mechanism involves activating the bacterial metabolism of nucleotides that the cells need to replicate their DNA.

There are dramatic energy demands placed on the cell as a result of the drug stress. These energy demands require a metabolic response, and some of the metabolic byproducts are toxic and help contribute to killing the cells,” said Dr. James Collins, the Termeer Professor of Medical Engineering and Science in MIT’s Institute for Medical Engineering and Science (IMES) and Department of Biological Engineering, and the senior author of the study.

Big agreements for Atomwise

Atomwise announces deals with Eli Lilly and Enamine

BY MEL J. YEATES

SAN FRANCISCO & KIEV, Ukraine—In early June, Atomwise Inc. disclosed a multiyear agreement with Eli Lilly and Co. to apply Atomwise’s patented artificial intelligence (AI) technology in support of Lilly’s preclinical drug discovery efforts. The companies will collaborate on up to 10 drug targets selected by Lilly, with the goal of accelerating the time it takes to identify and develop potential new medicines.

As continued on page 7

Aiming for antidepressants

TORONTO—A new project is underway that will pursue a novel rapid-acting antidepressant for treating major depressive disorder (MDD). This is the fifth collaboration under MaRS Innovation’s Lab150 partnership with Evotec SE, and includes the Centre for Addiction and Mental Health (CAMH), a MaRS Innovation member organization.

The focus of this collaboration will be to develop selective drugs that modulate channels tied to mediating emotional and stress responses, a key focus of the CAMH’s Dr. José Nobrega.

“Depression is a leading cause of death and disability around the world,” Nobrega noted. “Identification of new rapid-acting antidepressant treatments could have a major impact on the treatment of depression and the associated risk of suicide. The Lab150 opportunity allows my lab to conduct large-scale drug screening research with our Evotec collaborators, and represents a very significant step towards translating my research into a product of benefit to patients suffering from MDD.”

Machine learning reveals metabolic pathways disrupted by the drugs

CREDIT : ELI LILLY AND CO.
that result from this agreement. The company will also have the option to share equally in U.S. profits for certain products in select indications. Development costs for the profit share products will be shared in keeping with product rights.

“We are excited to partner with Gilead Sciences, a biopharmaceutical company known for its science-driven innovation and productivity,” said Dr. Tony Johnson, president and CEO of Goldfinch. “There is significant unmet need to improve health outcomes for patients with kidney diseases. This partnership will leverage Goldfinch’s KGA platform to identify new therapeutic targets and Gilead’s proven track record of efficiently advancing life-saving therapies for patients.”

For its part, Gilead will be granted exclusive options to license worldwide rights to certain products directed against targets identified by Goldfinch’s proprietary KGA registry of kidney disease targets. Goldfinch will apply its biology platform for this work, which consists of human induced pluripotent stem cell–derived kidney cells and kidney organoids to help validate targets.

Johnson notes that this is the first time the companies have worked together, though they have been in discussions for several months.

“Gilead really wanted to invest in the kidney, and I think that’s because chronic kidney disease is very prevalent, it’s deadly and it’s very, very expensive to the community—it costs about $8 billion a year for Medicare alone,” Johnson tells DDNews. “However, why they want to invest in us is, I think, primarily because we have our Kidney Genome Atlas coupled with our human biology platform, and these two together will help identify novel targets, all human genetics-driven.

In addition, they’ll help us validate those targets with our human biology validation system. That’s part A. Part B of why Gilead wanted to work with us is we’re applying a precision medicine approach to discovering and developing drugs for patients with kidney disease.”

At present, Johnson says, the KGA features 23,000 individuals, which includes patients with kidney disease as well as matched controls. All individuals have undergone whole-genome sequencing, as well as longitudinal and clinical phenotyping, and Goldfinch has also collected multiomics data—transcriptomic and proteomic data—on a subset. He notes that Gilead is interested in expanding it by another 80,000 participants, 40,000 of whom will have kidney disease and 40,000 of whom will be matched controls.

Goldfinch will expand the KGA to include diabetic kidney disease, identifying and validating targets as well as leading discovery and development activities prior to the exercise of any option rights by Gilead.

“Goldfinch has established unique genetic and biology platforms that will allow for the identification and validation of novel targets for kidney disease and for the discovery and development of novel compounds,” remarked Dr. John McHutchison, chief scientific officer and head of research and development at Gilead Sciences. “We look forward to partnering with our research collaborators at Goldfinch, as we seek to advance novel treatment options for people living with DKD and other serious kidney diseases.”

MIT

CONTINUED FROM PAGE 6

Exploiting this mechanism could help researchers to discover new drugs that could be used along with antibiotics to enhance their killing ability, the researchers say.

Collins and Dr. Graham Walker, an MIT professor of biology, have studied the mechanisms of antibiotic action for many years, and their work has shown that antibiotic treatment tends to create a great deal of cellular stress that makes huge energy demands on bacterial cells. In the new study, Collins and Dr. Jason Yang—an IMES research scientist and the lead author of the paper, which appeared in the May 9 issue of Cell—decided to take a machine-learning approach to investigate how this happens and what the consequences are.

Before they began their computer modeling, the researchers performed hundreds of experiments in E. coli. They treated the bacteria with one of three antibiotics—ampicillin, ciprofloxacin or gentamicin—and in each experiment, they also added one of about 200 different metabolites, including an array of amino acids, carbohydrates and nucleotides. For each combination of antibiotics and metabolites, they measured the effects on cell survival.

“We used a diverse set of metabolic perturbations so that we could see the effects of perturbing nucleotide metabolism, amino acid metabolism and other kinds of metabolic subnetworks,” Yang explained. “We wanted to fundamentally understand which previously undescribed metabolic pathways might be important for us to understand how antibiotics kill.”

Their model yielded the novel discovery that nucleotide metabolism, especially metabolism of purines such as adenine, plays a key role in antibiotics’ ability to kill bacterial cells. Antibiotic treatment leads to cellular stress, which causes cells to run low on purine nucleotides. The cells’ efforts to ramp up production of these nucleotides, which are necessary for copying DNA, boost the cells’ overall metabolism and leads to a buildup of harmful metabolic byproducts that can kill the cells.

The findings suggest that it may be possible to enhance the effects of some antibiotics by delivering them along with other drugs that stimulate metabolic activity. “If we can move the cells to a more energetically stressful state, and induce the cell to turn on more metabolic activity, this might be a way to potentiate antibiotics,” Yang said.

Adapted from an article written by Anne Trafton for the MIT News Office

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DISCOVERY

Accelerating antibiotics

Polyphor and the University of Zurich examine new class of drugs inhibiting the LPS transport pathway

BY DDNEWS STAFF

ZURICH—Polyphor and the University of Zurich (UZH) in Switzerland recently announced that Innosuisse, the Swiss Innovation Agency, had made a significant grant for the innovation project “Development of a new class of antibiotics inhibiting the lipopolysaccharide (LPS) transport pathway.”

The Innosuisse award will finance the salaries and material costs of Polyphor’s project partner UZH, whereas Polyphor will provide an additional contribution, of which a substantial part will be in kind. The research is independent from the project recently funded by Carb-X and the Novo Repair Fund.

The project funded by Innosuisse is based on a novel discovery of Prof. John Robinson and Prof. Oliver Zerbe from UZH concerning the molecular target and mode-of-action of the natural antimicrobial peptide thanatin. Thanatin inhibits the lipopolysaccharide transport protein A (LptA), which is critically involved in the transport of LPS from the periplasm to the outer membrane and of vital relevance to the bacteria.

Polyphor has discovered, through leveraging its macrocycle platform, a new class of antibiotics against gram-negative bacteria with a novel mode of action, which are called outer membrane protein targeting antibiotics, or OMPTAs. The most advanced drug candidate of this new class is murepavadin (POL7080), an antibiotic in clinical development targeting Pseudomonas aeruginosa, including its most resistant strains. It is followed by the next-generation OMPTAs (lead candidate: POL7056), now in advanced preclinical testing, which are medium-spectrum antibiotics targeting the most important gram-negative pathogens, including extensively drug-resistant and multidrug-resistant strains.

“This collaboration is a unique opportunity for the UZH and Polyphor to jointly develop antibiotics against priority gram-negative bacteria to treat infections with high unmet medical need,” said Oliver Zerbe, chief investigator of the project.

“We are delighted to have obtained the support from Innosuisse, which is a further proof of the potential of our technology platform,” added Daniel Obrecht, who is chief scientific officer and co-founder of Polyphor. “This project will allow us to continue a highly fruitful collaboration with the UZH which started in 2000.”

“As part of a recently inked agreement, Atomwise will have the option to develop compounds from the collaboration that Eli Lilly and Co. (pictured here) chooses not to advance into clinical testing.}

AI
CONTINUED FROM PAGE 8

According to Abraham Heifets, CEO and co-founder of Atomwise, “There is a mutual interest in working together to bring AI-powered drug discovery into the heart of preclinical drug development in Big Pharma. This is our first engagement together [with Eli Lilly], but with the excitement we’ve seen thus far in this partnership, it’s unlikely to be the last.”

Lilly is a recognized leader in virtual library design, with a massive number of molecules enabled by automated synthesis in their robotic laboratory. Identifying which molecules might be a potential new therapeutic for specific diseases is a scientific and analytical challenge, one that Atomwise’s AI technology is well suited for.

“We invented the use of a particular kind of machine learning—deep neural networks, which underpin all of the current revolution in practical AI—for structure-based drug design. Our technology uses a statistical approach that extracts insights from millions of experimental binding affinity measurements and thousands of protein structures to predict small molecules-protein binding affinities,” Heifets says.

“This fundamental tool makes it possible to do hit discovery and lead optimization and to make toxicity predictions with unparalleled precision. A key feature of the technology is that it makes it possible for our partners to efficiently test a large and diverse set of compounds, which enables the early identification of solutions to potential roadblocks in drug development.”

Heifets also states that “Lilly has made it clear that they are focused on developing drugs for novel targets, and therefore could be a key to unlocking success for patients.”

Atomwise could receive up to $1 million per target in discovery milestones and will be eligible for up to $550 million in potential development and commercialization milestones inclusive of all targets. As part of the agreement, Atomwise will have the option to develop compounds from the collaboration that Lilly chooses not to advance into clinical testing.

“We want to tackle novel and challenging targets with our current partners, including Eli Lilly, Bayer, UConn and DNDi, and new partners who are working on newly scratched the surface of what is possible—imagine what will be found when we screen a chemical library that is a thousand times larger.”

The 10-to-the-10 program will look at billions of compounds that have never been examined in any drug discovery program. By evaluating truly novel and structurally distinct compounds, the initiative also dramatically increases the likelihood of developing new drugs for existing targets, with fewer adverse effects. The enormous screen in the 10-to-the-10 program is possible because of a confluence of technologies: accurate and rapid structure-based drug development with Atomwise’s AI algorithms, scalable cloud computing...
The new collaboration to establish the Laboratory for Genomics Research builds off of work by the Innovative Genomics Institute, a UC Berkeley/UCSF nonprofit research center that is exploring ways to use CRISPR gene editing technology to improve public health.

**CRISPR**

**CONTINUED FROM PAGE 1**

Prof. Jonathan Weissman, University of California, San Francisco (UCSF), a pioneer of CRISPR screening technology and HHMI Investigator; and Dr. Hal Barron, chief scientific officer and president of R&D for GSK. This new laboratory will unite academia and industry members to pursue projects independently and in concert, with a focus on new technologies, drug targets and biological mechanisms. Key areas of interest will be immunology, oncology and neuroscience.

“Over the last seven years, CRISPR has transformed academic research, but until the LGR, we haven’t had a focused effort to catalyze the kind of research we know will lead to new innovation using this CRISPR tool,” said Doudna. “LGR is about building that space where creative science is partnered with the development of robust technology that will help develop tomorrow’s drugs. I think we’re going to be able to do science that none of us can even imagine today.”

Up to $67 million in funding will be provided for the LGR over the five years of the collaboration, which covers facilities for 24 full-time university employees funded by GSK and up to 14 full-time GSK employees. GSK’s artificial intelligence and machine learning group will play a role in establishing computational pipelines to enable analysis for the project. A joint steering committee—comprised equally of UC and GSK members—will govern the collaboration, with joint sub-committees overseeing issues such as patents, scientific and project management.

The ultimate goal, according to a GSK press release, “is to deepen our understanding of genetics and discover new targets, and to create next-generation technologies that will become future standard practice for the pharmaceutical industry.” The tools that the lab develops will be subject to intellectual property provisions, but they will also be available for use by other academic and non-profit labs, as per UC’s public mission.

“One of our key goals is to advance the field overall and make these tools as broadly available as possible. The LGR screening center will enable labs at UCSF and Berkeley, and having access to it will give our scientists opportunities to advance their research in ways that would be very hard for them to do in their own labs,” Weissman remarked.

“One of the biggest challenges that faces GSK—and frankly all of the pharma biotech industry—is that nine out of every 10 drugs, medicines, potential medicines that we begin clinical testing on fail to result in a treatment that can help a patient,” Barron commented in a video about the LGR initiative. “This field called functional genomics has been accelerated dramatically by one of the most innovative technologies in biomedical research in a long time, and that is CRISPR technology.”

“With the expertise of Jennifer and Jonathan helping to steer the LGR, I am confident the lab will significantly advance our scientific understanding of the relationship between genes and disease to help find better medicines faster,” he added in a statement.

This collaboration builds off of work by the Innovative Genomics Institute, a UC Berkeley/UCSF nonprofit research center co-directed by Doudna and Weissman that is exploring ways to use CRISPR to improve public health. So far, projects have included initial work toward a treatment for sickle cell disease, as well as “personalized and tissue-selective delivery of human therapeutics, improved plant varieties for environmental and agricultural uses, and new microbe-inspired biotechnologies,” according to the Institute’s website. In addition, it also focuses on providing education regarding the “scientific and societal implications of genome engineering,” important considerations in light of the recent developments of the infants subjected to CRISPR editing and the increased health risks that have appeared as a result.
Editorial: Off-target effect from inactives?

BY RANDALL C WILLIS

SOME OF YOU MIGHT REMEMBER when eggs were considered good for you. Then they were a risk to your cholesterol. Then they were good for you again. I’m not sure where the current consensus lies on the topic. Similiar controversy exists for things like red wine, various food oils, coffee...the list goes on and on. It hearkens back to the oft-recycled phrase “that many of us bring out when someone “helpfully” shares that something we enjoy causes cancer, and that is, “Doesn’t everything?”

The fact is that nothing, no matter how generally innocuous, is a true innocent. Much like we can cause harm to people’s well-being by speaking certain words or sharing certain news that we think is fine and pleasant or at least neutral, so too can just about anything hurt someone.

Earlier this year, the Massachusetts Institute of Technology (MIT) sent me an email that shared research about the inactive ingredients that constitute a hefty amount of most over-the-counter and prescription drugs. They are typically necessary to stabilize the drug or aid the-counter and prescription drugs. They are necessary to stabilize the drug or aid the-counter and prescription drugs. They are currently of unknown size, that will be extremely sensitive to those and develop symptoms triggered by the inactive ingredients,” said Daniel Reker, a Swiss National Science Foundation postdoc at MIT’s Koch Institute for Integrative Cancer Research and one of the lead authors of the study.

The researchers hope that their study, published in the March 13 edition of Science Translational Medicine, will raise awareness of this issue among patients and healthcare providers and help to stimulate reforms that could protect patients from drugs that they don’t tolerate well.

Right now there is an imbalance in the amount of information and understanding out there with respect to the inactive components of medication,” noted Giovanni Traverso, an assistant professor in MIT’s Department of Mechanical Engineering, a gastroenterologist at Brigham and Women’s Hospital and the senior author of the study.

“I’m definitely not against more information being available, and perhaps full ingredient lists on drug, including inactive ingredients, might be one way to help physicians and other healthcare folks to pin down when a drug may be harming a patient only because of a seemingly innocuous ingredient. Of course, the challenge is that people often don’t know when they are allergic to normal harmless substances. And even when they do, will we be able to pin down which drug has that substance in a form or amount that is enough to cause a problem?

In my family, allergies are a pretty common issue—mostly mild, but common. My co-parent has pretty serious year-round allergies but as she notes, “I can’t avoid the whole world, and it’s mostly the pollen out there that’s attacking me.”

Much as Randy Willis notes in his “Out of Order” commentary this month, drugs don’t always work as planned, and sometimes it’s the microbes in our bodies that make that happen. But adjusting our microbiome in response might not be the best idea. And finding a new drug that works better is often tricky.

And so, much like with genomics, I welcome the new insights and information. But let’s remember that sometimes, we can’t do much, even when we have lots of data and knowledge. Sometimes, things are just bad for some of us, and that cannot be helped. 

OUT OF ORDER: Inverted order?

WHEN I WAS A KID, coming home for lunch was a harrowing experience. Not because I lived in a bad neighborhood or because I was mistreated, but rather because I never knew what to expect when I walked through the door.

My mother, you see, simply could not leave the living room furniture alone. No sooner would I throw my jacket onto the chair than I would have to pick my jacket off the living room furniture alone. When I walked through the door.

Although my brothers and I were quite willing to watch television from any and all angles, my mother seemed incapable of relaxing in her environment and spent much of her day trying to make her environment fit her ever-shifting needs.

This memory was brought to the fore recently as I read a recent article of New Scientist (June 8-14), as it seems biomedical research and healthcare increasingly take on my mother’s traits. The magazine highlighted research undertaken by Yale’s Michael Zimmerman and colleagues to understand the potential influence of gut microbes on brain development.

“Given that the authors tested a broadly representative panel of drugs, the scale of these results is remarkable because it raises the possibility that most drugs are modified by the microbiota,” noted North-eastern University’s Kim Lewis and Holobiome’s Philip Strandwitz in an accompanying “News & Views” article. “This type of testing could also be a useful way of singling out drugs that would probably be deactivated by the microbiota.”

Within a fortnight of those publications, Harvard’s Yuval Mindel Rekal and colleagues published just such an effort in Science, where they screened gut microbes to identify two bacteria—Enterococcus faecalis and Eggerthella lenta—involvement in the metabolism of the Parkinson’s drug L-dopa to an inactive form. They then screened a series of tyrosine mimics and found one that could inhibit L-dopa metabolism in vitro. The compound also increased peak serum concentrations of L-dopa in mice colonized with E. faecalis.

Brilliant. Further evidence from well-designed experiments that gut microbes can metabolize the compounds we ingest, in some cases influencing therapeutic efforts.

Not to minimize the science in any way, but we have just described a living room of furniture and the functions of many individual pieces.

It is what comes later in the discussion, however, that reminds me of my mother’s domestic restlessness.

“The finding that our gut bacteria may affect so many drugs hints at the possibility of changing our microbial communities to increase a drug’s efficacy or reduce side effects,” wrote New Scientist’s Adam Vaughan. “The goal would be to change patients to suit their drugs, rather than the other way around.”

“Such issues highlight the complexity of considering a person’s microbiota when trying to take a personalized medicine approach,” wrote Lewis and Strawnitz. “Adjusting the microbiota to suit our needs, including achieving individually tailored approaches to tackling drug metabolism, is probably where this field is headed.”

“We have used chemical knowledge and interdisciplinary tools to decipher the molecular mechanisms by which gut bacteria interfere with the treatment of Parkinson’s disease,” Rekal and colleagues conclude.

In each case, there is an implication that the failure lies not with the drug(s), rather with the way we consider our needs, including achieving individually tailored approaches to tackling drug metabolism, is probably where this field is headed. We have used chemical knowledge and interdisciplinary tools to decipher the molecular mechanisms by which gut bacteria interfere with the treatment of Parkinson’s disease,” Rekal and colleagues conclude.

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WHILE THERE ARE TWO MARKETED PRODUCTS CURRENTLY, the excitement and investment generated in adoptive cell transfer (ACT) products are leading to a steep increase in the number and now the diversity of ACT products in clinical development. No longer the domain of autologous CD19 or BCMA constructs for blood cancers, we are in the world of tumor-infiltrating lymphocytes (TILs), allogeneic T cells, natural killer cells and other possible approaches in both blood and solid tumors.

WHY THE NEED FOR LONG-TERM FOLLOW-UP TRIALS?

Do we need long-term follow-up trials and is it really an issue? Well, although we are developing technologies that would allow for multiple infusion treatment regimens, most current technology is limited to a single or maybe just one secondary infusion.

Durability as well as response rates in the first wave of (potential) products have been impressive, but we know it is not the panacea yet, and some recent results with other large antibodies targeting CD19 are giving pause for thought when cost and logistical demands of ACT therapies are considered. However, the need to look at the long-term risks and benefits for patients who participate in ACT trials is paramount.

The fact is that with ACT therapy, the patient effectively becomes a genetically modified organism after administration, which in and of itself necessitates the length of follow up. It is often required by health authority regulatory guidelines per country, Germany being one example.

Study objectives are to demonstrate long-term safety and efficacy of subjects exposed to gene therapy medicinal products which are made with viral vectors, through monitoring of delayed adverse events related to ACT therapy including: persistence of the virus used in the manufacture of the product in the patient’s tissues (known as replication-competent lentivirus or RCL) or other viruses, if any, in the patient’s cells (we measure something called persistent vector sequences or PVS); and date of relapse, progression or death, if applicable.

All patients who have received an ACT infusion under a protocol should be asked to roll over upon either premature discontinuation from or completion of a study and participate in a separate long-term follow-up (LTFU) protocol for up to 15 years after their ACT infusion.

The data garnered from LTFU studies will likely be invaluable, but there are challenges which arise, along with some pointers to addressing those challenges, as addressed below.

THE CHALLENGES FACED

So, what are the main challenges posed by LTFU studies in ACT development? Patient retention is the first difficulty to countenance. Time is always of the essence. Cancer clinical trial patients commonly fall into the “previously failed prior therapy” category. Thus, they are primed and ready to quickly change direction if they are not responding to their current regimen and there are other treatment opportunities available.

This is certainly not unique to ACT studies but we are in risky waters, as more treatment options become available—especially in the ACT setting, we are seeing the reality of the challenge in real time. With patients needing to move on to other therapies as quickly as possible if they fail to respond to the investigational treatment and/or they have disease relapse, when a further experimental infusion is not possible, patients quickly remove themselves from one study in favor of another trial or other treatment, blurring the lines regarding safety profile and long-term effects.

With ACT there are real gaps in data sets for patient safety, tracking, patient outcomes/endpoint parameters resulting from, availability and quality of that data. For example, recognition of ACT associated toxicities such as B-cell aplasia (a condition that exposes the patients to infections) which might persist for up to one year. If one experimental therapy bleeds into another, both likely with limited safety data, there is the serious potential for blurred ACT data.

As mentioned earlier, LTFU data reporting is required by agencies so protocol compliance is key and yet difficult to achieve if, for example, physicians are looking to the next possible treatment for their patients.

There are the ethics of it all. Patients’ needs and new medical treatments quickly forces are ranged against participation and compliance in LTFU studies. In addition there are complications in reconciling the requirement to track patients with patient privacy concerns at sites.

PLUGGING THE HOLES

So, given that we need to plug holes in data gaps, programs are demanding it, what are the possible solutions for patient retention and protocol compliance, and how do we begin to deal with these factors?

We can discuss possible means of addressing challenges in the context of sponsors, contract research organizations (CROs) and sites. Sponsors and CROs need to engage regulators on this topic now, as this is not a protocol- or sponsor-specific risk. Obviously we need to secure commitment from investigational sites at the last trial we ran.

Beyond tumor cells and microenvironment, however, he also sees a significant role for the microbiome in cancer and other diseases.

My worry is that the microbiome will suffer guilt by association. Rather than simply see the gut microbiota as one more factor informing treatment decisions, we will see it as a target to be controlled with yet another drug.

In an interview for my last Special Report on Cancer, Agilent’s David Ferrick spent a lot of time talking about the concept of metabolic equilibrium. The success of cancer, he implies, is its effectiveness at creating a new equilibrium that works in its favor.

From his perspective, the mutations we associate with cancer don’t drive the disease to modify cells; persistence of ACT cells in the patient (we measure something called persistent vector sequences or PVS); and date of relapse, progression or death, if applicable.

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Amicus-Penn collaboration gains new life

Partners have expanded their agreement to include new indications and new research programs

BY KELSEY KAUSTEN

CHICAGO, ILL. & PHILADELPHIA—Capi-
talizing on momentum is the name of the game in a recent collaboration expansion, with Amicus Therapeutics and the Perel-
man School of Medicine at the University of Pennsylvania doubling the size of their exist-
ing partnership.

The collaboration, which was and still is aimed at researching and developing novel gene therapies, has been expanded from three programs for rare genetic diseases to six, and now includes Pompe disease, Fabry disease, CDKL15 deficiency disorder (CDD) and Niemann-Pick type C, as well as mucop-
loysaccharidosis type IIIB (MPS IIIB) and a next-generation program in mucopoly-
saccharidosis type IIA (MPS IIA)—both forms of MPS are known as part of Sanfil-
lipo syndrome.

Additionally, a discovery research agree-
ment has been established that grants Ami-
cus exclusive disease-specific access to rights to collaborate with Penn’s Gene Therapy Pro-
gram (GTP) to develop new gene therapy plat-
form technologies and programs for lysosomal disorders and 12 additional rare diseases.

“This agreement is a significant step forward in creating a world-class indus-
try-academia gene therapy partnership in rare diseases,” said Dr. James M. Wilson, Professor of Medicine and Pediatrics at the Perelman School of Medicine. “We have already seen highly encouraging preclini-
cal results and proof of concept in Pompe disease through our existing collaboration and are excited by what we can further achieve together.

“We are looking forward to expanding the relationship further for additional preclini-
cal programs and committing to the research required to further advance the technology platforms at Penn. We have seen the first results of our combined capabilities and platforms, and I believe that we can further expand and accelerate our efforts to rap-

dily develop gene therapies for many more patients with unmet needs.”

Harnessing bioprinted tissue to fight renal disease

SAN DIEGO—A collaboration has been launched between Organovo Holdings Inc. and Prof. Melissa Little at the Murdoch Children’s Research Insti-
tute, The Royal Children’s Hospital (Melbourne, Australia) and Ton Rabenink at Universiteit Leiden.

The partners are aiming to expand the use of 3D bioprinted stem cell-based therapeutic tissues to include approaches for treating end-stage renal disease. Funding for this undertaking comes from Stem Cells Australia and CSL Limited.

“Partnerships with world-class institutions can accelerate groundbreaking work in finding cures for critical unmet disease needs and the develop-
ment of implantable therapeutic tissues,” said Taylor J. Crouch, CEO of Organovo. “This collabo-
ration is another important step in this direction. With the devoted support of Stem Cells Australia and CSL Limited, leading researchers are able to leverage Organovo’s powerful bioprinting technol-
ogy platform to achieve significant breakthroughs.”

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A banner day for modeling

Q2 saw encouraging advances in disease modeling options

BY KRISTEN SMITH

NEW YORK & CAMBRIDGE, Mass.—May 28 featured notable news from two different companies working in disease modeling. TARA Biosystems and Centogene both released promising updates on their respective progress in moving modeling technology forward.

Disease modeling involves utilizing animal or human cells that display all or some of the pathological processes that are observed in the actual human or animal disease. Studying disease models aids understanding of how the disease develops and testing potential treatment approaches, especially in the search for rare disease therapies.

TARA Biosystems, based in New York, provides predictive, in-vitro human cardiac tissue models for use in drug discovery, safety assessment and translational medicine. The company offers a high-fidelity solution that is based on human stem cell-derived cardiac tissue matured to physiologically relevant adult-like levels and provides direct measures of cardiac functionality, including contractile force. TARA is dedicated to pioneering predictive cardiac tissue models that enable

MODELS CONTINUED ON PAGE 15

Collaboration center

Platform will help to characterize biotherapeutic products

BY ILENE SCHNEIDER

DARLINGTON, U.K.—The Centre for Process Innovation (CPI), a United Kingdom-based technology innovation center and part of the High Value Manufacturing Catapult, will collaborate with GlycoSelect UK Ltd., ForteBio-Molecular Devices and Allergan Biologics Ltd. to develop and integrate novel recombinant prokaryotic lectins (RPLs) into a biosensor-based platform to characterize and monitor the glycosylation of biotherapeutic products. Funded by Innovate UK, the glycan analysis platform can

CENTER CONTINUED ON PAGE 15
research programs in the Wilson Lab and to license select technologies developed under the auspices of the collaboration. Pompe disease, Fabry disease, CDD and an undisclosed rare metabolic disorder comprised the original program lineup for the agreement.

The next-generation research program will consist of a new five-year agreement under which Penn will conduct discovery research to develop new gene therapy technologies, while Amicus will continue to advance its own research and technology platforms to combine with Penn’s.

Per the terms of the agreement, Amicus will make a $10-million annual investment to GTP’s program each year for five years, with the possibility for an extension, and in return gains exclusive disease-specific rights to collaborate with GTP to research and develop products for lysosomal disorders. Amicus’ rights also cover rare diseases such as Rett syndrome, Angelman syndrome, myotonic dystrophy and certain other muscular dystrophies.

“The major expansion of the collaboration … is a bold move for Amicus, and it reflects our unwavering commitment to develop potential cures that may alleviate an enormous amount of suffering for many more thousands of people living with rare genetic diseases, many of them children. This collaboration also reflects the extraordinary scientific capabilities at Amicus, as well as the success that we have seen with the work that we have done in collaboration with Dr. Wilson and his team,” John F. Crowley, chairman and CEO of Amicus, noted in a conference call. “Stated simply, we see great value for patients and shareholders alike in aligning as strongly and as deeply as possible with Penn in these diseases.”

A key focus of this collaboration—before the expansion and continuing forward—is combining Amicus’ protein engineering and glycobiology work with Penn’s gene transfer technologies to enable novel gene therapies with better uptake, targeting, dosing, safety and manufacturability.

“Penn Medicine has put Philadelphia on the map as the global epicenter of gene therapy research and development, and under the leadership and vision of Jim Wilson, our expanded agreement with Amicus is an exciting milestone for a field which is in the midst of transformative breakthroughs,” remarked Dr. J. Larry Jameson, executive vice president of the University of Pennsylvania for the Health System and dean of the Perelman School of Medicine. “We are thrilled to be part of this collaboration, which will help to bolster our city’s growing reputation as a magnet for talent and an engine for gene therapy innovation.”

“With a globally approved precision medicine product for Fabry, a late-stage biologic product with breakthrough therapy designation for Pompe, and now the industry’s largest rare disease gene therapy pipeline, Amicus is well positioned to become a leading global biotechnology company at the forefront of human genomic medicine,” said Crowley.

“‘This agreement is a significant step forward in creating a world-class industry-academia gene therapy partnership in rare diseases,” says Dr. James M. Wilson, a professor in the medical school at the University of Pennsylvania. “We have already seen highly encouraging preclinical results and proof of concept in Pompe disease through our existing collaboration and are excited by what we can further achieve together.”

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Study finds that over 75 percent of genomic data is of European origin

BY DDNEWS STAFF

NEW YORK—More than three-quarters of genomic data is derived from people of European descent, leaving other ethnic groups understudied. To address this problem, researchers from the Icahn School of Medicine at Mount Sinai, the Fred Hutchinson Cancer Research Center in Seattle and a number of other academic centers have analyzed the genomes of nearly 50,000 non-European individuals to maximize genetic discovery and lessen clinical disparities.

As described in a paper published recently in *Nature*, this collaborative study revealed nearly 1,500 associations between genes and disease in minority populations, serving as a prime example of what racially inclusive research can bring.

The study, known as PAGE—Population Architecture using Genomics and Epidemiology—was founded by the National Human Genome Research Institute and National Institute on Minority Health and Health Disparities to research the correlation between genetics and disease in ethnically diverse individuals in the United States. In analyzing the genetic code of these diverse populations and comparing them to those of European descent, researchers identified 27 new genetic associations that have not been found previously in European populations, but have the potential to be transferable to other groups that share components of genetic lineage, such as African ancestry, which can be found in both African Americans and Hispanics/Latinos. Given that these two groups remain among the most understudied populations in genomic research, Mount Sinai and Fred Hutchinson researchers are left wondering what other ancestral associations remain undiscovered.

“To date, millions of genomes have been sequenced, but ethnic diversity remains an unmet need,” said Dr. Eimear Kenny, an associate professor of medicine and genetics at the Icahn School of Medicine at Mount Sinai, director of the Center for Genomic Health, and co-senior author of the publication. “Because the availability of non-European genomic data is limited, much of the existing clinical therapies disproportionately benefit those of European descent — further widening the health disparities gap.”

Added Dr. Christopher Carlson, an associate member of the Public Health Sciences Division at Fred Hutchinson and co-corresponding author of the publication: “Previous articles have alluded to the need for multi-ethnic diversity in genome-wide studies, but this study is among the first to clearly delineate the scope of the problem, using detailed analyses of minority genetic samples.”

As we enter an era of a more racially diverse America, the need to understand the genetic underpinnings of disease affecting traits or diseases, allowing the creation of Mini-Brains designed to study specific conditions.

As Kenny points out, “there is evidence that the inclusion of microglia in the Mini-Brain expands the capabilities of the platform to address neuroinflammatory disorders, which are increasingly seen as possible contributors to neurodegenerative diseases. The use of cells taken directly from consenting patients who have the diseases we research to create Mini-Brains furthers our ability to model diseases with genetic components, such as Alzheimer’s disease and amyotrophic lateral sclerosis. We believe that the Mini-Brain platform has broad potential to address a wide variety of neurological diseases.”

A NEED FOR DIVERSITY

MINI CONTINUED FROM PAGE 1

develop a new drug to an estimated $2.6 billion and more than 10 years. The problem is especially acute for neurological disorders like Alzheimer’s disease, amyotrophic lateral sclerosis and multiple sclerosis, where animals are notoriously poor predictors of human outcomes. The recent clinical trial failures of prospective Alzheimer’s drugs highlight the need for better and earlier ways to test drug candidates.

“Currently, there is a major disconnect in drug development between data generated during preclinical testing and the outcomes seen in human clinical trials. Simply put, animal biology is not human biology. Currently, animal testing remains the gold standard in the development of new drugs, despite the historical 89-percent failure rate of new drugs after translational testing based on positive animal and other preclinical data. Neurological drugs fail at an even higher rate: an estimated 94 percent,” Curley remarks. “AxoSim’s patent-pending Mini-Brain platform predicts human results, giving researchers a much better readout of which drugs are strong candidates for costly and time-consuming clinical testing, and it does so early in the development process.”

Related Nerve-on-a-Chip technology developed at AxoSim has been shown to achieve research milestones at a fraction of the time and cost of animal testing.

While our Nerve-on-a-Chip platform is a powerful way to assess how investigational drugs, chemicals and other factors affect human spinal and peripheral nerves, our Mini-Brain platform is a functional model of the human brain. It contains different types of crucial neuronal cells and support cells, as well as the neuron insulator myelin. The Mini-Brain platform is the only commercially available model of the brain with functional human myelin, which is critically important because disruption in myelin has implications in numerous pathologies,” states Curley.

The Mini-Brain platform creates tiny brain-like organoids for neuroscience research using human iPSCs stimulated in the laboratory to grow into brain cells, which are engineered to reproducibly form uniform spheres barely visible to the human eye. The Mini-Brain components interact with each other and their environment, and can be replicated on a large-scale. The cells used to create iPSCs can be harvested from healthy individuals or from volunteers with certain genetic disorders, which are increasingly seen as possible contributors to neurodegenerative diseases. The use of cells taken directly from consenting patients who have the diseases we research to create Mini-Brains furthers our ability to model diseases with genetic components, such as Alzheimer’s disease and amyotrophic lateral sclerosis. We believe that the Mini-Brain platform has broad potential to address a wide variety of neurological diseases.”

AxoSim mentioned that Hartung will serve as a consulting vice president of scientific affairs. Hartung is the Doerenkamp-Zbinden Chair for Evidence-based Toxicology and director of the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health. AxoSim also reported its acquisition of all the assets of Organome Inc., a company founded by Hartung to commercialize the Mini-Brain technology and other functional organ equivalents.

“It is our intention to expand this platform to ultimately address virtually all serious diseases involving the nervous system,” concludes Curley. “We intend to focus on several high-priority areas at first and add different disease capabilities as we grow. Dr. Hartung’s lab has validated the Mini-Brain as a platform for studying neurotoxicity and multiple sclerosis, which are also AxoSim’s primary initial applications.”

“A NEED FOR DIVERSITY: Study finds that over 75 percent of genomic data is of European origin” concluded Curley. “We intend to focus on several high-priority areas at first and add different disease capabilities as we grow. Dr. Hartung’s lab has validated the Mini-Brain as a platform for studying neurotoxicity and multiple sclerosis, which are also AxoSim’s primary initial applications.”

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develop a new drug to an estimated $2.6 billion and more than 10 years. The problem is especially acute for neurological disorders like Alzheimer’s disease, amyotrophic lateral sclerosis and multiple sclerosis, where animals are notoriously poor predictors of human outcomes. The recent clinical trial failures of prospective Alzheimer’s drugs highlight the need for better and earlier ways to test drug candidates.

“Currently, there is a major disconnect in drug development between data generated during preclinical testing and the outcomes seen in human clinical trials. Simply put, animal biology is not human biology. Currently, animal testing remains the gold standard in the development of new drugs, despite the historical 89-percent failure rate of new drugs after translational testing based on positive animal and other preclinical data. Neurological drugs fail at an even higher rate: an estimated 94 percent,” Curley remarks. “AxoSim’s patent-pending Mini-Brain platform predicts human results, giving researchers a much better readout of which drugs are strong candidates for costly and time-consuming clinical testing, and it does so early in the development process.”

Related Nerve-on-a-Chip technology developed at AxoSim has been shown to achieve research milestones at a fraction of the time and cost of animal testing.

While our Nerve-on-a-Chip platform is a powerful way to assess how investigational drugs, chemicals and other factors affect human spinal and peripheral nerves, our Mini-Brain platform is a functional model of the human brain. It contains different types of crucial neuronal cells and support cells, as well as the neuron insulator myelin. The Mini-Brain platform is the only commercially available model of the brain with functional human myelin, which is critically important because disruption in myelin has implications in numerous pathologies,” states Curley.

The Mini-Brain platform creates tiny brain-like organoids for neuroscience research using human iPSCs stimulated in the laboratory to grow into brain cells, which are engineered to reproducibly form uniform spheres barely visible to the human eye. The Mini-Brain components interact with each other and their environment, and can be replicated on a large-scale. The cells used to create iPSCs can be harvested from healthy individuals or from volunteers with certain genetic disorders, which are increasingly seen as possible contributors to neurodegenerative diseases. The use of cells taken directly from consenting patients who have the diseases we research to create Mini-Brains furthers our ability to model diseases with genetic components, such as Alzheimer’s disease and amyotrophic lateral sclerosis. We believe that the Mini-Brain platform has broad potential to address a wide variety of neurological diseases.”

AxoSim mentioned that Hartung will serve as a consulting vice president of scientific affairs. Hartung is the Doerenkamp-Zbinden Chair for Evidence-based Toxicology and director of the Center for Alternatives to Animal Testing at the Johns Hopkins Bloomberg School of Public Health. AxoSim also reported its acquisition of all the assets of Organome Inc., a company founded by Hartung to commercialize the Mini-Brain technology and other functional organ equivalents.

“It is our intention to expand this platform to ultimately address virtually all serious diseases involving the nervous system,” concludes Curley. “We intend to focus on several high-priority areas at first and add different disease capabilities as we grow. Dr. Hartung’s lab has validated the Mini-Brain as a platform for studying neurotoxicity and multiple sclerosis, which are also AxoSim’s primary initial applications.”

“A NEED FOR DIVERSITY: Study finds that over 75 percent of genomic data is of European origin” concluded Curley. “We intend to focus on several high-priority areas at first and add different disease capabilities as we grow. Dr. Hartung’s lab has validated the Mini-Brain as a platform for studying neurotoxicity and multiple sclerosis, which are also AxoSim’s primary initial applications.”
CPI researchers will collaborate with GlycoSeLect, ForteBio-Molecular Devices and Allergan Biologics to develop and integrate novel recombinant prokaryotic lectins into a biosensor-based platform to characterize and monitor the glycosylation of biotherapeutic products.

**CENTER**

CONTINUED FROM PAGE 12

reduce costs and accelerate product development pipelines to deliver safe and efficacious medicine to patients, according to CPI.

The collaboration addresses the need for new analytical approaches to satisfy the growing biotherapeutics market. While biotherapeutics have been demonstrated to be effective in treating numerous diseases, their development is expensive, technically challenging and risky. Because more than two-thirds of biotherapeutics exist in a glycosylated form, the glycan profile needs to be monitored throughout product development and manufacture.

CPI uses applied knowledge in science and engineering, combined with state-of-the-art development facilities, to enable its clients to develop, prove, prototype and scale up the next generation of products and processes, according to Dr. John Liddell, chief technologist. The organization’s open innovation model allows clients to develop products and prove processes with minimal risk. CPI provides assets and expertise that gives its collaborators the opportunity to demonstrate the process before investing substantial amounts of money in capital equipment and training. Thus, according to CPI, new products and processes can be shown to be feasible on paper, in the lab and in the plant before being manufactured on an industrial scale.

As Liddell explained, “By utilizing proven assets and expertise, companies can take their products and processes to market faster. There is no down time in production, as all of the process development is completed offsite, and our technology transfer and engineering teams can help companies to transfer the product or process into full-scale production at speed.”

Founded in 2004, CPI aims to streamline development and manufacturing of biotherapeutic products throughout the cGMP manufacturing and analytical development services to biotech and pharmaceutical customers. Services include expression system development, analytical and quality control, process development, strategic advice, training, regulatory affairs, technical troubleshooting and clinical trial supply logistics.

Using GlycoSeLect’s glycan recognition technology and ForteBio-Molecular Devices’ biosensor-based analytical platform technology, the collaboration developed an assay platform to define the glycosylation profiles of biotherapeutics. The ForteBio-Molecular Devices’ Octet instrument detected interactions between GlycoSeLect’s RPLs and biotherapeutic proteins from Allergan Biologics.

Validated by the consortium partners, the assay platform established linearity of response, limits of detection, robustness, reproducibility and specificity. In addition to enabling real-time analysis, it was determined to be effective on both purified and in-process biotherapeutic proteins.

Combining GlycoSeLect’s RPLs with Bio-Layer Interferometry-based assay technology, the analytical platform was determined to be quick and cost-effective. It can be used with high-throughput process development and in-process control approaches to enable glycans characterization of a biotherapeutic product throughout development and manufacturing phases. A

**MODELS**

CONTINUED FROM PAGE 12

faster, safer and more reliable development of new medicines.

On May 28, the company announced an exclusive worldwide license agreement for intellectual property relating to engineered human heart tissues. The relevant technology was developed at Columbia University in the laboratory of Dr. Gordana Vunjak-Novakovic, a leader in the field of engineering functional human tissues for regenerative medicine—she is also one of the most highly cited individuals across all scientific and engineering disciplines.

“We are very pleased to enter into this exclusive license with TARA, which has been a core part of the rapidly growing NYC life-sciences startup ecosystem,” said Orin Herskowitz, executive director of Columbia Technology Ventures, the technology transfer arm of Columbia University. “We are excited to be a part of TARA’s current and future success.”

Together with a former trainee, Dr. Milica Radišić, Vunjak-Novakovic co-founded TARA Biosystems. Radišić developed the patented Biowire II platform, for which TARA is the exclusive worldwide licensee, which propels TARA’s modeling work in search of cardiac health and drug discovery.

“I have great confidence in the TARA team and their ability to deliver on the promise of our intellectual property,” commented Vunjak-Novakovic. “We are inspired by the same mission to help improve the lives of patients and their families through safer and more effective therapies.”

Meanwhile, in Massa-chusetts, Centogene released a promising white paper detailing the efficacy of its induced pluripotent stem cells (iPSC) program in accelerating drug development for rare and orphan diseases. The company has amassed some 500 skin biopsies from patients affected by a number of rare metabolic diseases, which are challenging to procure by virtue of their rarity. The exciting promise is that Centogene’s library of iPSC cells representing numerous rare diseases can be used as a critical tool for drug discovery through pharmacological partners. A significant challenge in orphan drug development for rare genetic diseases is the lack of predictive high-throughput compound screening systems, with animal-based disease models often unsuitable and primary patient cells, such as neuronal and cardiac cells, difficult to obtain.”

Dr. Arndt Rolfs, CEO of Centogene, in an in-house iPSC program for orthogonal target validation as well as further biomarker discovery.

Both TARA Biosystems and Centogene are adding to a global framework to study disease progression and treatment, generating key models to foster and facilitate research from various angles. Such innovative disease modeling tools will allow innovators at universities, pharmaceutical companies and other scientific research companies to drive the research forward.

**TOOLS & TECHNOLOGY**

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PRECLINICAL

STEM-ULATING RESEARCH

Two branches of stem cell research discovered the impact on both diabetes and cardiac damage

BY MEL J. YEATES

STEM CELLS are enjoying a renaissance lately, and preclinical research is applying them to everything in sight—from Alzheimer’s disease, eye diseases and cancer to orthopedics, Parkinson’s disease and stroke therapy.

One new study elucidates how adipose-derived stem cells can improve metabolic balance. Meanwhile, at the Icahn School of Medicine at Mount Sinai, researchers have recently discovered that placental stem cells from mice can target heart injuries, and start to repair damage.

An article in Experimental Biology and Medicine suggests a new therapeutic strategy for type 2 diabetes and obesity. The study led by Dr. Bing Wang, a professor in the department of general surgery at Shanghai Ninth People’s Hospital and Shanghai Jiao Tong University School of Medicine in China, reports that transplantation of adipose tissue-derived mesenchymal stem cells (ADSCs) improves metabolic balance and reduces inflammation in an animal model.

Sedentary lifestyles, along with high-fat and sugar diets, have increased the prevalence of diabetes. The World Health Organization estimates that 49 percent of the 347 million people worldwide with diabetes have type 2 diabetes (T2D). Obesity can be a contributing factor for T2D diabetes, and the inflammation that occurs in obesity exacerbates insulin resistance.

A preliminary clinical study showed that transplantation of mesenchymal stem cells improves metabolic balance in patients with T2D. ADSCs are abundant and can be harvested with minimally invasive procedures, but their ability to improve metabolic function in T2D or obesity was not known.

In the new study, Wang and colleagues assessed the ability of ADSCs to alleviate insulin resistance in high-fat diet (HFD)-fed mice. HFD-fed mice receiving ADSCs exhibited reduced blood glucose levels.

Researchers at the Icahn School of Medicine at Mount Sinai discovered that stem cells derived from the placenta—known as Cdx2 cells—can regenerate healthy heart cells after heart attacks in animal models. Pictured here is the Icahn Medical Institute.

Potential to treat Pompe disease

Findings validate gene therapy approach

BY IRENE SCHNEIDER

CRANBURY, N.J.—Pompe disease, a fatal neuromuscular and motor neuron disorder, affects 5,000 to 10,000 people worldwide. Caused by deficiency of the enzyme acid alpha-glucosidase (GAA), the inherited lysosomal storage disorder can lead to the accumulation of glycogen in cells.

The debilitating disease is characterized by severe muscle weakness that worsens over time. Pompe disease ranges from a rapidly fatal infantile form significantly impacting heart function to a more slowly progressive, late-onset form primarily affecting skeletal muscle. Respiratory and cardiac failure are the leading causes of morbidity and mortality.

Amicus Therapeutics, a biotechnology company focused on discovering, developing and delivering novel high-quality medicines for people living with rare metabolic diseases, is collaborating with the Gene Therapy Program of the Perelman School of Medicine at the University of Pennsylvania (Penn) to develop a novel gene therapy for Pompe disease. The proposed therapy combines the Amicus protein-engineering and glycochemistry expertise with Penn’s adenos associated virus (AAV) gene transfer technologies. Amicus announced initial preclinical data from its investigational AAV gene therapy program for Pompe disease in mice at a poster session entitled “Development of a Novel Gene Therapy for Pompe Disease: POTENTIAL TO TREAT POMPE DISEASE CONTINUED ON PAGE 18

Immunotherapies vs. infections

Breakthrough research identifies a potential vaccine against deadly fungus

BY JIM CIRIGLIANO

LOS ANGELES—Researchers at the Los Angeles Biomedical Research Institute (LA BioMED) and Vitalex Biosciences announced in June a successful experiment studying a mucormycosis immunization in mice that protected against the fungal infection. The result of the experiment gives hope for the possibility of a comparable immunotherapy for humans against serious infections caused by fungi in the family Mucorales, which are on the rise and often fatal.

LA BioMed’s Dr. Ashraf Ibrahim, a professor of medicine at the University of California, Los Angeles, and the founder of Vitalex Biosciences, led a team of 12 researchers in the development of several polyclonal and monoclonal antibodies against conserved peptide regions of the CotH3 protein, which is universally present in Mucorales. CotH3 protein allows the fungus to invade host tissues to cause infection.

“This line of research goes back to 2008-2010,” says Ibrahim. “At the time, we identified CotH3 as the fungal component that allows Mucorales to bind to host cells via the GpR78 protein. We were interested in blocking this process from happening, to see if we can help mice overcome the infection.”

“When we looked into the protein sequence of CotH3, we found it was encoded by an orthologous gene in the fungus and that a single nucleotide insertion was responsible for the altered protein.”

The team proposed a vaccine containing a truncated version of CotH3, which has been shown to elicit long-lasting immunity in animal models.

Researchers identified a particular epitope within CotH3 that induced high levels of antibodies against the protein, providing protection against lethal mucormycosis infections in mice.

“Results from our preclinical studies have shown that the vaccine is well-tolerated in mice and induces high levels of antibodies,” Ibrahim said. “We are now preparing to file an Investigational New Drug application with the U.S. Food and Drug Administration to begin clinical trials.”

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STEM CELLS

Stem-celling research
and enhanced insulin sensitivity, ADSCs overexpressing neuregulin 4, a growth factor with beneficial effects in obesity and T2D, were the most effective in reducing blood glucose and insulin resistance.

“Our study shows that neuregulin overexpression could improve the efficacy of ADSCs in ameliorating insulin resistance and other obesity-related metabolic disorders and may provide a new therapeutic strategy for the treatment of obesity, insulin resistance and T2D,” said Wang, senior author of the study.

These protective effects were due to the suppression of inflammation and augmentation of glucose uptake in skeletal muscle and adipose tissues. Collectively, these studies demonstrate that ADSC transplantation improves glucose tolerance and metabolic balance in HFD-fed mice by multiple mechanisms.

Dr. Steven R. Goodman, editor-in-chief of Experimental Biology & Medicine, pointed out that “Wang and colleagues have provided a potential new therapeutic option for type 2 diabetes who are obese. If future clinical trials using this approach are efficacious, this will provide a valuable new treatment for type 2 diabetes.”

And not long ago in May, researchers at the Icahn School of Medicine at Mount Sinai discovered that stem cells derived from the placenta known as Cdx2 cells can regenerate healthy heart cells after heart attacks in animal models. Cdx2 cells can migrate through the circulatory system and target heart injuries. Once there, the cells transform into beating heart cells and start the repair process.

The findings, published in Proceedings of the National Academy of Sciences (PNAS), could represent a novel treatment for cardiac regeneration. Researchers were able to isolate Cdx2 cells from full-term human placentas too, raising the possibility of being able to harvest the treatment from placentas that would normally be discarded, noted principal investigator Dr. Hina Chaudhry, director of Cardiovascular Regenerative Medicine at the Icahn School of Medicine at Mount Sinai.

“Cdx2 cells have historically been thought to only generate the placenta in early embryonic development, but never shown to have the ability to regenerate other organs, which is why this is so exciting. These findings may also pave the way to regenerative therapy of other organs besides the heart,” added Chaudhry. “They almost seem like a super-charged population of stem cells, in that they can target the site of an injury and travel directly to the injury through the circulatory system and are able to avoid rejection by the host immune system.”

The Mount Sinai research team had previously discovered that a mixed population of placental stem cells helped the hearts of pregnant female mice recover after an injury that could otherwise lead to heart failure. The current study aimed to determine what type of stem cells made the heart cells regenerate. The investigators looked at Cdx2 cells, and found them to comprise the highest percentage (40 percent) of those assisting the heart from the placenta.

To test the Cdx2 cells’ regenerative properties, the researchers induced heart attacks in three groups of male mice. Magnetic resonance imaging was used to analyze mice immediately after the heart attacks, and three months after induction with cells or saline. They found that every mouse in the group with Cdx2 stem cell treatments had significant improvement and regeneration of healthy heart tissue. Three months post-treatment, the stem cells had migrated directly to the heart injury and formed new blood vessels and cardiomyocytes.

Researchers found that Cdx2 cells have all the proteins of embryonic stem cells, and additional proteins which give them the ability to travel directly to the injury site—something embryonic stem cells cannot do. Cdx2 cells also appear to avoid the host immune response, and did not reject the cells when administered from the placenta to another animal.

“These properties are critical to the development of a human stem cell treatment strategy, which we have embarked on, as this could be a promising therapy in humans. We have been able to isolate Cdx2 cells from term human placentas also; therefore we are now hopeful that we can design a better human stem cell treatment for the heart,” explained Chaudhry. “Past strategies tested in humans were not based on stem cell types that were actually shown to form heart cells, and use of embryonic stem cells for this goal is associated with ethics and feasibility concerns. Placentas are routinely discarded around the world and thus almost a limitless source.”

“These results were very surprising to us, as no other cell type tested in clinical trials of human heart disease was ever shown to become beating heart cells in petri dishes, but these did and they knew exactly where to go when we injected them into the circulation,” stated first author Dr. Sageeetha Vadakke-Madathil, postdoctoral fellow in medicine (cardiology) at the Icahn School of Medicine at Mount Sinai.

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IMMUNO

Two separate preclinical efforts recently point to the continuing promise of stem cells: first with research that shows adipose-derived stem cells can improve metabolic balance, and second with work that has demonstrated that placental stem cells from mice can target heart injuries and repair cardiac damage.

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Researchers at the Los Angeles Biomedical Research Institute (LA BioMED) and Vitalex Biosciences are on a path to perhaps create an immunization against the fungal infection mucormycosis. Pictured here is Dr. Keith Hoffman, LA BioMED’s vice president of business development and technology transfer.

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

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STEM

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IMMUNO

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Two regions of the Mucorales organisms that cause mucormycosis. Furthermore, mice treated with a combination of the Ca antibody and a common antifungal drug most universally survived the infection, and most had recovered and appeared healthy by the end of the study. These recovered mice showed no residual fungi in the lungs or brains. The researchers are optimistic that their discovery could lead to the development of preclinical immunotherapies in humans.

The antibodies in the study were of mouse origin, and thus will need to be adapted to the human immune system. Ibrahim’s team plans to modify the structure of the antibodies through a process called antibody humanization in order to allow them to function properly in humans.

Mucormycosis is caused by several fungi in the Mucorales family, including Rhizopus, Mucor and Lichtheimia. It has gained attention for its rise in U.S. transplant centers in recent years, as well as for an outbreak of infection in France, in which cases rose by 70 percent in a nine-year period. Infection of these fungi have mortality rates ranging from 90 percent to 100 percent.

“This is mainly a disease of the immunosuppressed patients,” explains Ibrahim, including patients with poorly controlled hyperglycemia, diabetics, hematologic malignancy patients, neutropenic patients due to cancer treatment, and transplant patients.

“All of these patients are increasing in numbers every year due to the advancement in cancer treatment and transplantations, and due to increased cases of diabetes,” he says. “A steady and alarming rise in mucormycosis cases has been noticed over the past two decades, and is predicted to continue increasing.”

Mucormycosis also strikes some patients who suffer severe injuries due to major trauma, such as soldiers injured in combat and vehicle accident victims.

Beyond reversing the underlying predisposing factors for the disease whenever possible, there are currently three small-molecule agents used for treating mucormycosis: lipid formulations of amphotericin B, isavuconazole and posaconazole. Surgical removal of the infected foci is a final option, but can involve a disfiguring surgery to remove necrotic tissues. This is the first immunotherapy to specifically target mucormycosis and engage the patient’s immune system to recognize and kill the invading fungus, according to Ibrahim.

“Immunotherapies have made real difference in cancer and inflammatory disease management, and it is the time now for them to be used in managing infectious disease more widely than they are used now,” he remarks.

EDITCONNECT: E071914

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The rodents shall remain

Rats and mice expected to continue as most lucrative species for animal models

BY DDNEWS STAFF

According to a compiled study from Future Market Insights titled “Animal Model Market: North America to Lead in Terms of Revenue Through 2026,” the global animal model market will reflect an impressive compound annual growth rate through the forecast period 2017 to 2026, with revenues poised to surpass $2.2 billion by the end of 2026.

Key takeaways from the report include:

- North America is expected to remain the largest and fastest-expanding market for animal models, with the other growing markets—in order of higher growth to lower growth—being Asia-Pacific, Europe, Latin America and the Middle East/Africa region.
- On the basis of species, revenues from rats and mice are projected to account for over a two-fifths share of the market by the end of 2026, though the revenues from use of cats and monkeys in animal models will rise at a comparable rate. Dogs and pigs are expected to remain the least lucrative species used in animal models during the forecast period.
- Contract research organizations and biotechnology companies are anticipated to remain the fast-expanding end-users of animal models.
- Basic and applied research applications of animal model will continue to register the fastest expansion through 2026. However, the drug discovery/development will remain the most lucrative application of animal models.

Key companies contributing to growth in this market include Transgenoap Biopharmaceuticals, Envigo, Crown Bioscience, Eurofins Scientific, Genoway, Taconic Biosciences, Trans Genic, The Jackson Laboratory, Horizon Discovery Group and Charles River Laboratories International.

POMPE

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Engineered Acid Alpha-Glucosidase Transgene for Improved Expression and Muscle Targeting” at the American Society of Gene & Cell Therapy 22nd Annual Meeting in Washington, D.C.

As explained in the poster session, the current standard of care, enzyme replacement therapy (ERT), is limited in improving muscle function and unable to cross the blood-brain-barrier, causing progressive neurologic deterioration in long-term survivors of classic infantile Pompe disease. ERT using recombinant human GAA (rhGAA) delivered every other week by intravenous infusion is the only approved treatment available for Pompe disease. To be effective, rhGAA must be internalized in target muscle cells and delivered to lysosomes at clinically relevant doses. Maintaining both efficacy and safety has proven difficult.

According to Dr. Hung Do, chief science officer of Amicus, these very important preclinical results validate our capabilities to develop engineered GAA proteins that can efficiently correct target cells and tissues via a gene replacement therapy for Pompe disease. This approach may be applicable to other lysosomal disorders as we continue to combine our Amicus protein engineering expertise, together with Penn’s vector engineering expertise, to develop novel gene therapies.

The Amicus/Penn Pompe hGAA AAV gene therapy program builds upon the protein engineering and manufacturing expertise used to successfully develop AT-GAA, Amicus’s late-stage enzyme replacement therapy-chaperone treatment paradigm. It demonstrated more uniform cellular uptake and lysosomal targeting compared to natural hGAA AAV gene therapy.

In addition, the engineered hGAA AAV gene therapy demonstrated robust glycogen reduction in all key tissues in Pompe disease that were examined. In the central nervous system, the engineered hGAA AAV gene therapy reduced glycogen significantly in neuronal cells, indicating that it could be an effective method of addressing neuronal aspects of Pompe disease. Conversely, natural hGAA AAV gene therapy did not reduce glycogen in neuronal cells.

Thus, initial findings validate the Amicus/Penn collaboration and the potential of this platform to enhance protein targeting across multiple lysosomal disorders. Further preclinical studies to evaluate this engineered hGAA with various doses and routes of AAV administration are underway.

“Developing a potential cure for Pompe has been a personal and professional goal for many years,” said John F. Crowley, chairman and CEO of Amicus. “These data are profound, and it is extremely rewarding to see these preclinical results that show our Amicus-engineered GAA is optimized for uptake into target tissues and gets to the right cellular compartments, especially in the central nervous system.”

John F. Crowley, chairman and CEO of Amicus Therapeutics

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Representatives of Amicus Therapeutics at the closing bell of NASDAQ in 2014. Some of the company’s preclinical research suggests it might be on the road to finding an effective treatment for Pompe disease.

For more information, visit www.DDN-News.com
Very often, early in-vitro and preclinical successes of drug candidates fail to translate into human gains. To help address this issue, there is growing interest in the exploration of less-defined phenotypic impacts in drug screening.

By Randall C Willis

At one night, a police officer approaches a man frantically searching the ground under a streetlight.

“Did you lose something?” the officer asks.

“Yes, my car keys,” the man replies. The officer assists in the search but after a few fruitless minutes, begins to wonder.

“Are you sure you lost them here?” the officer asks.

“No, I lost them in the park,” the man replies, not giving up.

“The park’s a block away,” the officer retorts. “Why are you looking here?”

The man finally looks up: “Because this is where the light is.”

Microscopy meets the molecular in the search for phenotypic impacts in drug screening.
SCREENING
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The ability to characterize human disease down to a malfunctioning enzyme or receptor or to a single mutated gene has led to an era of aggressively targeted therapeutics. This era has seen significant successes, but it has also seen numerous failures, where early in-vitro and preclinical success has failed to translate into humans. It is not that the therapeutic is not hitting its assigned target. The problem is often instead that it is hitting its target and one or more unanticipated targets, or that its intended target has pleiotropic (affecting two or more phenotypic traits) effects.

When you look for what you seek, you may find it, but you may miss other equally important facets of the equation.

To address this limitation of defined molecular endpoints, there is growing interest in the exploration of less-defined phenotypic impacts in drug screening.

BEYOND THE STREETLIGHT

Sam Cooper, co-founder of Phenomic AI, highlights the difference by comparing BRAF mutation-driven cancer vs. fibrosis.

“When you know the mutation, you can create a drug unique to that mutated form,” he says. “But if you look at fibrosis, the condition is probably not that genetic.”

“When you don’t understand the genetics of it and you can’t nail it down to a single protein, there are probably a lot of proteins going wrong at the same time,” he continues. “That is where the phenotypic approach works really well.”

Understanding what is happening in a cell, tissue or organism during disease evolution, or in a drug screen, means seeing as much as possible as openly as possible. And it means having as much physiological context as possible for the model being examined.

“When phenotypic screens, you can see if the compound is having the preferred effect regardless of what the target is,” explains Coo- per’s colleague and co-founder Oren Kraus. “You can also probe toxicity and other facets directly in one assay.”

Although phenotypic analysis has been a mainstay of drug development since the earliest days of medicine—think Galen surveying patient symptoms, or pathologists bunched over histology slides—it is only recently that the methods and technologies have started to achieve a throughput to rival biochemical assays.

“I used to be a bench researcher and ran a core facility for a number of years on the academic side,” says Brendan Brinkman, now senior marketing manager at Olympus Life Sciences. “I have really seen the trajectory of the way things have advanced in the last 10 to 15 years; some of it is breathtaking.”

“We’ve had real increases in sensitivity and speed on the microcopy side, but also a more sophisticated understanding of the context-dependency of physiological responses to drugs,” he adds.

It is well understood, he explains, that cells in 3D culture or in tissues behave very differently from cells in 2D culture. Concomitant with that understanding has been the development of optical technologies to unravel what’s happening in those 3D contexts and the ability to translate the increasingly complex data arising from those experiments into meaningful information.

Brinkman is quick to point out the synergistic importance of molecular techniques, however—not just highlighting the multiplexing technologies for which his industry is known, but also the ability to manipulate cells and tissues with tools like the gene-editing technology and techniques known as CRISPR.

“This convergence of fundamental technologies is really leading to a significant increase in the potential for phenotypic screens, which can now begin to couple in things that were only available in a purely molecular type of analysis previously,” Brinkman enthuses. “Where you might extract cell populations and analyze the kinds of molecules that were in those cell populations, even on a single-cell level, we can now look at those cells and tissues in their context while we’re treating them with various drugs. That’s a real game-changer for us.”

Reflecting the importance of context, Purdue University’s Sherry Voytik-Harbin and colleagues described their efforts to develop a 3D tumor invasion model for high-throughput, high-content phenotypic drug screening. In a 96-well format, they suspended small clumps of pancreatic ductal adenocarcinoma (PDAC) tissue within a matrix of cancer-associated fibroblasts.

The researchers then monitored the impact of gemicatibin on tumor invasion using multiplex assays defining cell parameters such as number, proliferation and metabolic activity.

“Observations that gemicatibin is effective at inhibiting proliferation while not fully eradicating the tumor or hindering invasion is consistent with its mechanisms of action as targeting DNA synthesis,” the authors noted. “Additionally, these results align with those from PDAC xenograft models, which show gemicatibin substantially hinders tumor growth and proliferation but does not induce significant apoptosis or reduction of distinct metastases and invasion-related markers.”

Perhaps more importantly, however, the researchers were keen to note that these results highlighted the need to extend screening assays beyond simple assessments of cell viability or cytotoxicity, to quantify a variety of phenotypic parameters.

“Those kinds of things are really only possible in a live-cell context or at the very least, in a context where you can see the cells interacting with each other in a very clear way,” he says.

Late last year, David Drubin and colleagues at University of California, Berkeley and Howard Hughes Medical Institute examined precisely this question, undertaking what they called 4D cell biology to study clathrin-mediated endocytosis (CME) in stem cell-derived intestinal organoids.

To monitor vesicle movement within the organoids, the researchers fluorescently tagged two CME proteins. Furthermore, to correct for tissue-induced aberrations, they used adaptive optics with lattice light-sheet microscopy.

“The large 3D field of view allowed us to image through the organoid’s epithelial cell layer and to capture Ctr1 and Dm2 dynamics on apical, basal and lateral membranes with a frame rate of 2.85 s/frame per channel,” the authors wrote. “The field of view allowed the simultaneous observation of multiple cells at a time.”

The sheer volume of data, however, required that they also develop a package of image and data analysis tools: open-source
microscopy, the researchers could induced liver injury. They could be useful in predicting drug-organ chips. In particular, they and Emulate performed similar biology, they concluded. For tissue-scale 4D quantitative cell image analytics can open the door advanced microscopy and big data cell biology, 3D organoid culture, and noted a significant treatment effect, including changes to mitochondrial structure. Similar analysis of apoptosis-inducing staurosporine produced increases in an apoptosis marker. For the researchers, the results speak to something deeper than historical limits. But even here, there have been turn to model organisms, such as rodents and non-human primates. To address this challenge and to open drug screening efforts to more serendipitous discovery—whether positive or negative—researchers turn to model organisms, such as rodents and non-human primates. But even here, there have been historical limits. “In this case, ethical concerns arise, and, from a practical point of view, these animals are expensive and their handling is labor-intensive.” Martin Gijs and colleagues at École Polytechnique Fédérale de Lausanne suggested recently, “Thus, these studies cannot involve a high number of specimens, which prevents any high-throughput experimentation.” These challenges were part of the group’s rationale for performing their systemic screening efforts in the nematode Caenorhabditis elegans.

From their perspective, the worm offered several attractive features as a model system: • Small size makes it easy and inexpensive to grow; • Fewer ethical concerns than with mammals; • Transparency facilitates whole-body imaging; • Shares many genes in common with humans; • Genetic manipulation protocols are available (e.g., siRNA, CRISPR); and • Complete cell lineage has been mapped from fertilized egg to adult. C. elegans is the only organism you can study at the speed of in-vitro cell culture, if you have the right systems,” offers Adela Ben-Yakar, founder of Newormics and researcher at the University of Texas at Austin. Building that “right system” has been the mission of Ben-Yakar and colleagues for several years now. “My journey started about 15 years ago,” she recounts. “We were using lasers to do axotomic injured axons and for the first time, we could see nerve regeneration in C. elegans.” “Of course, it was a long and very laborious process,” she continues. “You had to immobilize the C. elegans, then find where they were immobilized, then perform the imaging.” An engineer by training, and given that the worms were cultured in liquid medium, Ben-Yakar realized that microfluidics might be the solution. “There were a couple of other groups who were doing this, and we were all creating these really fancy and complex microfluidic platforms that enabled immobilization of C. elegans at high resolution at better and higher throughput than what we did manually,” she remembers. “But these were still a very small number of animals.” Furthermore, the devices were so complicated, she recalls, that it would take a long time for even an engineering student to master it.
SCREEnING
CONTINUED FROM PAGE 21
As Ben-Yakar indicated in a review earlier this year, the optimal microfluidic system needed to...

...Be compatible with automated platforms, such as liquid handling and robotics systems;...

...Eliminate cumbersome interfaces, such as multiple inputs and complex tubing manifolds;

...Provide a sufficient number of samples (animals) per test in a limited space; and

...Immolize the animals close to the imaging optics and orient them in their optically favorable side for high-resolution imaging.

Using these criteria as a template, Ben-Yakar’s group developed the vivoChip, a 96-well format microfluidic platform imaged on an inverted microscope.

Late last year, Ben-Yakar and colleagues described their efforts to apply the vivoChip to a screen of compounds targeting amyloid precursor protein-induced neurodegeneration. In earlier work, the group developed a C. elegans model that carried a single copy of the sigma 2 receptor, aka transmembrane protein 97.

Gijs and colleagues, for example, recently described their chip-based screening platform and automated image analysis. Lower throughput than the vivoChip, the Swiss platform divides larger channels into small corridors, each of which holds a handful of freely swimming worms, grown from larvae.

As a proof of concept, the researchers monitored the response of worms to different concentrations of doxycycline, taking images every 20 minutes for 52 hours. Specifically, they examined the antibiotic’s impact on growth using bright-field imaging and on oxidative stress using GFP expression and fluorescence imaging.

“Worms that were treated with doxycycline showed slower growth and increased GFP expression compared with untreated worms,” the authors noted. “These results indicate that a higher mitochondrial stress may affect and delay the development process.”

They then performed a motility assay in real-time using a stereomicroscope with dark-field illumination, monitoring the worms’ drosophila response to the anaesthetic tetrathiomethylene. Interestingly, the researchers noted subtle differences in the response times of different worms experiencing the same treatment, highlighting the importance of single-worm resolution analysis.

The implications of the experiments were multiple, according to the authors.

“Once the image-based readout was established, the automated pipeline enabled the screening and profiling of a library of 1,280 compounds in thousands of embryos in about one year,” the authors wrote. “As the work relies on a simplified module for advanced feedback microscopy workflows and accessible open-source image-processing techniques, we believe this pipeline can serve as an example and template for biomedical research labs with limited resources that aim to conduct large-scale phenotypic scoring in a whole organism model.”

Clearly, the throughput and timelines with zebrafish are not yet as good as those with C. elegans, but progress is being made.

As more and larger model systems are being explored, however, technical advances are not simply required on the optics and husbandry side of things. As suggested earlier, expansion of these technology areas have led to an exponential growth in data, requiring novel analytical resources.

DElUGED IN DATA
Automated microscopy enables capturing multiple features including real-time to more adequately assess the full response to drug treatment,” Ocell0’s Leo Price and colleagues recently noted in a review of 3D cell-based drug screens. “The greater morphological complexity of tissues cultured in 3D makes this type of high-content analysis particularly valuable, retrieving rich information that would be overlooked by single endpoint assays.”

Capturing multiple xy images in a 3D experiment, sometimes over multiple image channels, can dramatically increase data volumes over a comparable 2D experiment, the authors suggested. To cope with this, many software platforms adjust 3D stacks to 2D.

“A lot of the screening tools grew up in the 2D world,” explains Olympus’ Brinkman. “Even when you have confocal-type technology, which is just looking at optical sections, these 3D volumes of data might be compressed down into a maximum-intensity projection;
we call it a 3D data.”

“It loses all of the information about spatial distribution, it changes the accuracy of cell counts, and ultimately, it changes things like ID390 responses,” he continues. “You get different drug dosage results, specifically depending on how you measure it, whether you’re measuring in 3D or 2D.”

For this reason, Price and colleagues explained, OcellIO developed its own in-house software to permit true 3D phenotypic analysis and single-cell segmentation.

Commercially, a similar effort at Olympus resulted in NovoSight, which the company launched in the United States last September.

“It wasn’t so easy to automatically identify objects in three dimensions and quantify their volume across not only a single field of view or single image data set, but also across a whole experiment within a microplate,” Brinkman explains. “You’re doing segmentation analysis across all of these different structures—nuclei, mitochondria, whole cells or even whole organoids/spheroids—and yet that kind of analysis was extremely difficult.”

“What we set out to do was to find a way to improve the object recognition with specific kinds of 3D algorithms, and create a graphic user interface that made that really accessible and deliver results that were informed by our expertise in the optical field to make sure that the accuracy was as high as possible,” he adds.

And much as Newormics’ Ben-Yakar talked about developing screening systems that could be used without a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering, so too is Brinkman adamant about data analysis tools not requiring a degree in engineering. 

BRIGHT FIELDS AHEAD

So, where is the intersection of phenotypic and molecular analysis going next? Brinkman laughs.

“I have to be a little careful about that,” he chuckles. “I am a strategy guy and an inventor, so I can’t say too much explicitly.”

“Clearly, we need to continue to pursue technologies that allow us to image cells and tissues in a physiologically relevant way,” he continues. “We need to do that faster. We need to do it more accurately.”

And, he adds, we need to start looking at the possibilities of manipulating cells and tissues genetically, not only through traditional approaches based on such things as CRISPR technology that can allow us to really test hypotheses.

“This definition of cell manipulation technology with the ability to view cells and tissues in a physiological context, those kinds of technologies are really going to be the future of drug discovery,” he explains.

“We’re getting to the convergence of being able to recapitulate certain physiological responses, not only in microtissues or organs-on-a-chip or bodies-on-a-chip, and that’s coming together with the ability to analyze the data in more meaningful ways and more reproducible ways,” Brinkman reflects. “It’s a really exciting time for the field.”

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SPECIAL REPORT

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**BRIEFS**

**Valneva’s VLA15 study continues apace**

SAINT-HERBLAIN, France—Valneva SE’s Phase 2 study for VLA15 has moved into the main study phase, with an independent data safety monitoring board clearing two dosage levels for clinical development. VLA15 is being evaluated as a Lyme disease vaccine, and in a Phase 1 trial, it presented with a favorable safety profile, was immunogenic in all doses and formulations tested, and triggered a strong anamnestic response after a booster vaccination administered 12 to 15 months after initial immunization. The company intends to launch another Phase 2 study to investigate an alternative immunization later this year.

“We are pleased that the run-in safety data confirm our hypothesis that we can proceed with higher doses than initially studied in Phase 1. Given the well-understood mode of action, high anti-OspA antibody titers are key to deliver a highly effective vaccine that will address the significant unmet medical need arising from the increasing spread of Lyme disease,” commented Dr. Wolfgang Bender, chief medical officer of Valneva.

**Initial data encouraging for ixiladencel**

STOCKHOLM—Immunicum AB (publ) recently shared positive top-line results from its Phase 1/2 clinical trial, which evaluated the safety and tolerability of ixiladencel in combination with tyrosine kinase inhibitors in six patients with gastrointestinal stromal tumors (GIST). Ixiladencel demonstrated a favorable safety profile with no fatal treatment-related adverse events and no autoimmunity. The compound also showed signs of clinical benefit, with two patients presenting with a partial response to treatment in which tumor growth stopped and partially regressed for three months and six months, respectively.

“There is a considerable achievement to see partial response in two out of six advanced-stage GIST patients as the disease at that point has developed resistance to standard of care treatment with TKIs,” commented Dr. Robert Bränström, the study’s principal investigator.

**If at first you don’t succeed...**

Despite setback with IFX-1, InflaRx continues testing

BY KRISTEN SMITH

PLANKING, Germany—InflaRx is reporting mixed results about their keystone drug candidate, IFX-1, a first-in-class monoclonal anti-human complement factor C5a developed to block the behavior of C5a with an attraction towards its target in human blood. According to the company, this is significant in that “IFX-1 leaves the formation of the membrane attack complex (C5b-9) intact as an important defense mechanism, which is not the case for molecules blocking the cleavage of C5. IFX-1 has been demonstrated to control the inflammatory response driven tissue and organ damage by specifically blocking C5a as a key ‘amplifier’ of this response in preclinical studies.”

While it is believed to be the first monoclonal anti-C5a antibody introduced into clinical trials for ilixadencel

Representatives of InflaRx at NASDAQ in 2017 after the company became listed on the exchange.

**Imago unveils IMG-7289**

Safety and efficacy data inform expansion of study into Phase 2b

BY MEL J. YEATES

SAN FRANCISCO—Imago Biosciences Inc. announced in June that positive safety and early efficacy clinical data regarding its lysine-specific demethylase (LSD1) inhibitor, IMG-7289, were presented at the 24th Congress of the European Hematology Association.

According to Dr. Hugh Young Rienhoff, Jr., CEO of Imago Biosciences, “IMG-7289 is an inhibitor of the epigenetic enzyme lysine-specific demethylase 1, which regulates differentiation in maturing blood cells. LSD1 is a remarkable enzyme that regulates many of the key features of hematopoiesis, such as stem cell self-renewal, differentiation and growth. Inhibition of the enzyme appears to be very safe if one monitors blood counts. In malignant myeloid cells, LSD1 is required for high expression of inflammatory cytokines such as interleukin 8.

“In addition, IMG-7289 may have uses outside of hematologic disease, given that it causes tumor cells to become more immunogenic. This was an unanticipated finding and suggests that there is much more to learn about LSD1 and its inhibition outside of oncology.”

The data from the ongoing IMG-7289-CTP-102 Phase 1/2a clinical trial showed that IMG-7289 was well tolerated in patients with high or intermediate-2 risk myelofibrosis that was resistant to or intolerant of approved therapy. The therapy **CONTINUED ON PAGE 25**

**Design in the cloud**

Exploristics announces launch of KerusCloud 2.0

BY DDNEWS STAFF

BELFAST, Northern Ireland—In mid-June, data analysis and clinical trial software specialist company Exploristics announced plans to launch an updated version of its cloud-based data analytics platform for clinical trial design, KerusCloud 2.0. Plans at the time called for release by the end of the summer.

The software offers what the company calls “unique second-
clinical development, the results in ongoing clinical trials are tepid. Approximately 300 people have been treated with IFX-1 in clinical trials, and the antibody has been shown to be well tolerated. IFX-1 is currently being developed for various inflammatory indications, including hidradenitis suppurativa (HS), ANCA-associated vasculitis and pyoderma gangrenosum.

Earlier this month, the company released the top-line results for the SHINE Phase 2b trial of IFX-1, which they hoped would be for people with HS, an orphan skin disease with limited effective treatment. The company was disappointed to report that their study showed that IFX-1 had no significant dose response.

“Unfortunately, we had to report a failure on the analysis of the primary endpoint (dose-dependent effect of IFX-1 on the [Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16) of the trial, while we reported a statistically significant effect of IFX-1 on the Dermatology Life Quality Index and a trend in AN count reduction (AN = abscess and inflammatory nodule count) when compared to placebo treatment,” asserted a statement from the company. “The DLQI was originally used (amongst other parameters) to validate the HiSCR.

After 16 weeks, with 179 patients at over 40 sites, researchers looked at the HiSCR and found no significant response, especially since the placebo arm showed an unusually high response rate in the study. This was anomalous to placebo results from other studies, signifying the need for in-depth analysis of the validated full data set for the initial placebo-controlled double-blinded part of the first four months of the SHINE trial.

Othmar Zenker, chief medical officer of InflaRx, said: “We are disappointed that we were not able to demonstrate a significant signal on dose response for the treatment with IFX-1. While we are still analyzing additional data, we note that the trial demonstrated an unusually high placebo HiSCR rate at week 16.”

Despite these disappointing results, the company continues to explore the potential of IFX-1, not just in trying to better understand this recent data but also delving into other diseases. InflaRx is also testing IFX-1 on other rare but debilitating auto-immune diseases, including anti-neutrophil cytoplasmic antibodies, or ANCA-associated vasculitis, and related acute inflammatory processes. Likewise, as the company noted in another June news release, they have treated the first patient suffering from pyoderma gangrenosum (PG) in their Phase 2a clinical trial.

PG is an uncommon, but devastating, neutrophil-driven, auto-inflammatory disease, typified by severe ulcerated pustules under the skin, predominantly on the legs. Its cause is not fully understood, but patients with PG have demonstrated elevated immune mediators. The exact prevalence of PG is not yet known, but it estimated to impact one per 100,000 people.

InflaRx is engaged in an open-label Phase 2a proof-of-concept study which will eventually enroll approximately 12 patients with moderate to severe PG, initially in Canada. Patients will be treated with IFX-1 for 12 weeks with a three-month follow-up period.

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Novavax confirms accelerated approval pathway available for licensure of NanoFlu

**BY DDNEWS STAFF**

GAITHERSBURG, Md.—Novavax Inc., a late-stage biotechnology company developing next-generation vaccines for serious infectious diseases, announced recently that it will utilize the accelerated approval pathway for licensure for NanoFlu, its nanoparticle seasonal influenza vaccine candidate. The U.S. Food and Drug Administration (FDA) acknowledged in a recent letter that the accelerated approval pathway is available to Novavax for its NanoFlu vaccine.

Furthermore, Novavax expects to initiate its pivotal Phase 3 clinical trial by the fall of 2019, with top-line clinical data expected in the first quarter of 2020. These immunogenicity data are expected to support a U.S. biologics license application (BLA).

Novavax will conduct an end-of-Phase 2 meeting with the FDA in the third quarter of 2019 to discuss the proposed Phase 3 clinical trial design and other topics that will support the future BLA. The accelerated approval pathway enables Novavax to conduct a non-inferiority immunogenicity clinical trial against a licensed quadrivalent comparator, with a commitment to confirm efficacy post-licensure.

“NanoFlu’s encouraging results observed in prior clinical trials, which demonstrated improved immune responses against licensed comparators, provide us confidence in the future success of the Phase 3 clinical trial,” said Dr. Gregory M. Glenn, president and CEO of Novavax. “The accelerated approval pathway allows us to potentially obtain U.S. licensure more expeditiously, and ideally, deliver a greatly needed improved flu vaccine, which could reduce the tremendous medical and economic burden of influenza.”

“The accelerated approval pathway, combined with the strategic partnership we announced ... with Catalent Biologics, allow us to efficiently and cost-effectively complete the clinical development of NanoFlu through BLA and licensure,” added Stanley C. Erck, president and CEO of Novavax. “The Catalent deal provides an $16 million cash infusion and flexible manufacturing capacity, supported by the experienced professionals transferred from Novavax to Catalent.”

Earlier this year, Novavax released positive top-line results of its Phase 2 clinical trial of NanoFlu in older adults. The data showed NanoFlu induced improved immune responses when compared to the best-selling flu vaccine in the older adult market. The Phase 2 clinical trial compared the safety and immunogenicity of various quadrivalent formulations of NanoFlu with or without the Matrix-M adjuvant with two licensed influenza vaccines in 1,375 healthy older adults. All formulations of NanoFlu were well tolerated and elicited vigorous immune responses to the four strains included in the vaccine. NanoFlu also demonstrated significantly improved hemagglutinin inhibition antibody responses against wild-type H3N2 viruses, including drifted strains when compared to Fluzone High-Dose, the leading flu vaccine in older adults.

**IMAGO**

CONTINUED FROM PAGE 24

was also effective in reducing spleen volumes and substantially improved symptom scores in a majority of evaluable patients.

“IMG-7289 has shown tremendous promise to be a meaningful treatment option for myelofibrosis patients, and these data support our clinical program,” says Rienhoff. “These data, particularly the strong safety and efficacy signals, have informed our Phase 2b dosing strategy and encourage us to explore additional indications in myeloproliferative diseases.”

The data presented were from a cohort of 16 enrolled patients, 15 of whom had received one or more prior treatments, including ruxolitinib. All patients began treatment with a sub-therapeutic dose of 0.25 mg per kg, with doses increasing until platelet count rested between 50 and 100K/µL.

Twelve patients (75 percent) sustained a platelet count within this target zone at a dose of 0.81 mg/kg, with 14 patients (88 percent) completing the 85-day study. Nine patients were evaluable for efficacy, with six (66 percent) showing a reduction of spleen volume via imaging and five (56 percent) recording a greater than 50 percent reduction in total symptom score and two (22 percent) recording an improved bone marrow fibrosis score at 12 weeks.

“The only approved treatment for myelofibrosis (MF) is ruxolitinib, an inhibitor of the JAKs and JAK2 kinases which are at the proximal end of a pathway signaling growth of blood cells. The basic therapeutic thesis for treating MF with IMG-7289 is to tame the mutant megakaryocytes which make many of the protein factors that drive the clinical aspects of the disease,” Rienhoff notes.

The study has not shown safety signals, dose-limiting toxicities or patient deaths with a median duration of treatment at 156 days. Fourteen patients in the study reported a total of 239 adverse events. There were 15 serious adverse events, only one of which was deemed related—painful splenomegaly.

“Even with a conservative dosing approach to evaluate safety, we saw encouraging improvements in patients’ symptoms and spleen sizes,” mentioned Dr. Kristen Pettit, assistant professor of medicine at the Rogel Cancer Center at The University of Michigan and a principle investigator of the study. “Continued evaluation of this therapeutic candidate under the modified clinical trial design with a more aggressive dosing approach will be a critical next step. We look forward to continuing evaluation of this therapeutic candidate under the modified clinical trial design with a more aggressive dosing approach.”

Based on the findings, Imago has expanded the study into a Phase 2b trial and is evaluating clinical investigations in additional myeloid diseases. The expanded study, which is expected to enroll 35 additional patients, will utilize a modified dosing schedule of IMG-7289 that safely optimizes efficacy. Additional trial sites have been added in the U.S., EU and U.K.

“With the safety, PK and dose-response data in hand, the principle features of the Phase 2b protocol focus on documenting efficacy and clinical benefit, which include reduction in spleen volume, improvement in symptom scores and quality of life, and a reduction of bone marrow fibrosis and tumor load,” notes Rienhoff. “Among other changes, the amended protocol allows for longer uninterrupted treatment (24 weeks) and a higher starting dose. The patient population and the clinical assessments remain the same.”

When asked about the next steps for IMG-7289, Rienhoff tells DDNews that, “IMG-7289 will be studied for the treatment of polycythemia vera, essential thrombocythemia. It may also be effective in sickle cell anemia and thalassemia intermediata. In combination with other agents, IMG-7289 will be studied in patients with acute myeloid leukemia and solid tumors.” He adds that Imago will “finish enrollment of the 2b study, begin the studies in polycythemia vera and essential thrombocythemia in 2019 and consider the merits of initiating other clinical studies in 2020.”

**IMAGO may have uses outside of hematologic disease, given that it causes tumor cells to become more immunogenic,” says Dr. Hugh Young Rienhoff, Jr., CEO of Imago BioSciences. “This was an unanticipated finding and suggests that there is much more to learn about LSD1 and its inhibition outside of oncology.”**
For more information, visit www.DDN-News.com

**CLINICAL TRIALS**

**DESIGN**

CONTINUED FROM PAGE 24

generation simulation capabilities, providing a virtual environment for optimizing clinical study design and data analysis through the processing power of cloud computing.”

First launched in 2018, KerusCloud is currently the only software available that can simulate trials with multiple correlated outcomes, according to Exploristics, allowing it “to untangle the complex relationships between the many biological factors that can influence a study’s outcome. Its cloud-based approach makes the simulation of complex studies an affordable and accessible option regardless of project size.”

KerusCloud 2.0 builds on its previous incarnation by reportedly enabling more realistic clinical trial simulations thanks to a new feature that generates correlated data for subgroups within a patient population, facilitating the investigation of precision medicine or adaptive development pathways. This means that clusters of patients in a clinical trial grouped by factors such as genetics, risk factors and biological subtypes can be looked at in greater detail, enabling clinical development teams to pursue more complex clinical strategies with high-silico design tools.

The latest version also delivers an enhanced user experience with simulations that are said to be 96 times faster, allowing users to explore a greater range of options in a much shorter time period. In addition, increased security features have been added, such as multi-factor authentication.

“We’ve already witnessed the profound difference KerusCloud can make to our customers’ clinical trials, with one customer saving $25 million and three years’ development time in their clinical development strategy,” said Dr. Aiden Flynn, CEO of Exploristics. “The updated KerusCloud 2.0 puts clinical development teams at the forefront of complex study design by supporting key decision-making to optimize and accelerate clinical development strategies.”

To support KerusCloud 2.0, Exploristics will be offering enhanced consulting services with a dedicated team of experts available to help ensure that customers can reap the full benefit of the new version as they confront the challenges of increasingly complex clinical scenarios.

Continued Flynn: “Removing barriers to state-of-the-art clinical trial planning is vital to transforming global clinical practice and improving the quality of clinical research, and we believe KerusCloud 2.0 will play a key role in that.”

The platform has even caught the attention of the government, with Exploristics recently awarded a £1 million Innovate UK loan to extend its capabilities by integrating it into an intelligent software ecosystem. »

**NKF**

CONTINUED FROM PAGE 1

Kidney and Blood Pressure Center at Tufts Medical Center.

“For the first time we will have a comprehensive collection of patient data which will enable us to better design patient education resources, more targeted care and more patient-centered clinical trials to discover new treatments for the disease,” noted Dr. Kerry Willis, chief scientific officer for the National Kidney Foundation. “There is no other kidney disease registry in the world that combines patient-entered data with data from electronic health records, and this pivotal combination will provide us with a 360-degree view of the patient we are working to help.”

The NKF Patient Network will collect and concentrate a variety of data, including medical history, demographics, diet, lifestyle, disease stage and related comorbidities, as well as laboratory values for diagnostic tests and medications. Ultimately, the goals are to offer patient education and support; centralize a diverse group of patients for clinical trial recruitment and trial design input; and establish a database of patient information and outcomes to support research, treatment and policy decisions.

“As we break virtual ground on the NKF Patient Network, there is much to be learned over the next year as we undertake what will be a distinctive resource to help advance the field of CKD [chronic kidney disease] research and patient care,” commented Inker. “A diverse and highly innovative team will be focused on developing the NKF Patient Network and making it into a powerful, yet easy-to-use, online platform that will serve generations of patients and researchers.”

The network will be developed over the course of the next year by PulseInfoFrame, work that will include testing the registry’s patient portal and a feasibility study to test the links to electronic health record data from individual patients and a large-scale health system partnership.

The full-scale launch of the platform, including large-scale patient recruitment, is expected in February 2020, with a global launch set for 2021. Foundational support for this program comes from a collaboration with Bayer AG.

Patient recruitment for clinical trials is currently the leading reason for trials not being completed on schedule, and that is no less true in the field of kidney disease. According to Inker, the hope for this project is that it will not only educate patients, but also educate trial sponsors as to new options for trial design and boosting recruitment.

“If patients are aware of what the meaning of kidney disease is, then we can try and engage them in the interest of participating in clinical trials. That will help recruitment, and that will allow the whole drug development process to go much easier than it currently is,” says Dr. Lesley Inker, chair of the NKF Patient Network Steering Committee.

**“For the first time we will have a comprehensive collection of patient data which will enable us to better design patient education resources, more targeted care and more patient-centered clinical trials to discover new treatments for [kidney] disease.”**

Dr. Kerry Willis, chief scientific officer for the National Kidney Foundation pool of really engaged, interested participants, patients who are interested in participating in trials or in research in many other ways, may help facilitate the performance of clinical trials. We talk about having patients engaged to help design trials, what does it mean to be a research participant, and having engaged patients who can even help us design trials that are better for patients is part of what our aims are.”

Approximately 30 million adults in the United States are estimated to have chronic kidney disease, with one in three adults at risk for the disease, and most are unaware of their disease state. Risk factors include diabetes, high blood pressure, obesity, heart disease and a family history of kidney disease. »
It’s never just been about killing or removing tumors; it’s about aiming at them accurately

BY JEFFREY BOULEY

PRECISION MATTERS. Sure, you could bake those cookies for twice as much time as called for to make sure they’re done, but then you’ll have ash-flavored, tooth-cracking little bricks. You could take out a single person with a missile, but that doesn’t bode well for the rest of the people all around. You could literally bathe in sunscreen before heading out to the beach, but your hair will be greasy and your eyes surely will sting.

And so it has been with so many cancer treatments that have either not gotten to all of the cancerous cells, leaving room for recurrence, or damaged healthy cells in the process, leading to all kinds of nasty side effects.

Researchers and others in healthcare, life sciences and elsewhere understand this, and fortunately many of them are trying to change the landscape of treatment to be more friendly to humans and less so to tumors.

CONFINING CELL-KILLING TREATMENTS TO TUMORS

Late June saw news from the Massachusetts Institute of Technology (MIT) that researchers at the Koch Institute for Integrative Cancer Research at MIT have developed a technique to prevent cytokines from escaping once they have been injected into the tumor, by adding a Velcro-like protein that attaches itself to the tissue.

You see, cytokines, small proteins released by immune cells to communicate with each other, have for some time been investigated as a potential cancer treatment. But while they have known potency and potential for use alongside other immunotherapies, these proteins are highly toxic to both healthy tissue and tumors.

And that is where the MIT research comes in, because while injecting the cytokine treatment directly into the tumor itself could better target the tumor and spare healthy tissue, previous attempts to do this have resulted in the proteins leaking out of the cancerous tissue.

And so it was that the researchers, led by Dane Wittrup, MIT’s Carbon P. Dubbs Professor in Chemical Engineering and Biological Engineering and a member of the Koch Institute, discovered a collagen-binding protein called lumican, which they then attached to the cytokines.

“When we inject (a collagen-anchoring cytokine treatment) intratumorally, we don’t have to worry about collagen found elsewhere in the body; we just have to make sure we have a protein that binds to collagen very tightly,” said lead author Noor Momin, a graduate student in the Wittrup Lab at MIT.

To test the treatment, the researchers used two cytokines known to stimulate and expand immune cell responses. The cytokines, interleukin-2 (IL-2) and interleukin-12 (IL-12), are also known to combine well with other immunotherapies.

“In addition, all of the cytokine therapies were given alongside a form of systemic therapy, such as a tumor-targeting antibody, a vaccine, a checkpoint blockade or chimeric antigen receptor T cell therapy, as we wanted to show the potential of combining cytokines with many different immunotherapy modalities,” Momin says.

The researchers now plan to carry out further work to improve the technique, and to explore other treatments that could benefit from being combined with collagen-binding lumican. Ultimately, they hope the work will encourage other researchers to consider the use of collagen binding for cancer treatments, Momin remarks.

NODDING TO NEOANTIGENS

Tumor-specific neoantigens, which arise via mutations that alter amino acid coding sequences, can be expressed on the surface of tumor cells and subsequently recognized by T cells. Normal tissues don’t express these particular mutations, and thus immuno-oncology therapies based on neoantigen-specific T cells should pose no harm to normal tissues.

Ziopharm Oncology Inc., a clinical-stage immuno-oncology company developing next-generation cell and gene therapies, recently announced an exclusive licensing agreement with the National Cancer Institute of the US to test its gamma-913 (also known as gamma-9) neoantigen-targeted cancer vaccine. The target antigens are derived from the patients’ own tumors.

“By harnessing a patient’s cancer-specific cellular immune response to their own tumor, this approach has the potential to offer individualized treatment for patients,” says Dr. Eugene Flaherty, chief scientific officer at Ziopharm.

By testing Ziopharm’s vaccine alongside immune checkpoint inhibitors, Flaherty hopes to increase its efficacy. Both methods, he says, “may allow for effective treatment even for patients that lack a robust immune response.”
MIT researchers, in two separate studies, have found a way to keep a potential cancer therapeutic approach from leaking out of tumor cells, and have figured out how to better target ovarian cancer cells both for surgical removal and potential diagnostic applications.

National Institutes of Health for neoantigen-related intellectual property related to the development and commercialization of cell therapies for cancer.

Under the terms of the agreement, Ziopharm is granted rights to two groups of technologies for use with the company’s Sleeping Beauty platform. The first group of technologies covers intellectual property related to T cell receptors (TCRs) reactive to mutations, or neoantigens, within KRAS, p53 and EGFR gene families. Alterations within these genes are referred to as “hotspots,” as the genetic changes can be driver mutations found in multiple types of solid tumors and between individuals with the same cancer type.

The second group includes manufacturing methods and processes to generate large numbers of Sleeping Beauty-modified T cells expressing high levels of the introduced neoantigen-specific TCRs.

“This license significantly expands our library of neoantigen-specific TCRs against hotspots and provides additional enhancements to our manufacturing capabilities for clinical-grade T cells through our Sleeping Beauty platform,” said Dr. Laurence Cooper, CEO of Ziopharm. “We are pleased to finalize this licensing agreement with the NCI, which is a result of our ongoing collaboration with Dr. Rosenberg and his team and enhances our shared efforts to pursue a non-pharmacologic approach to cancer treatment.”

Also related to neoantigens, Genocea Biosciences Inc., a biopharmaceutical company developing personalized cancer immunotherapies, announced in May a research collaboration with Iovance Biotherapeutics Inc. to explore the utility of ATLAS, with its ability to identify and characterize neoantigens, in developing neoantigen-targeted TIL therapies, which would naturally complement our ongoing personalized cancer vaccine and cell therapy programs.

Also from Genocea came news in June of best-in-class clinical results from its ongoing Phase 1/2a trial for GEN-009, the company’s lead neoantigen vaccine candidate. The company noted that in the five patients for whom immune response results are available to date, GEN-009 monotherapy elicited T cell responses to 91 percent of the vaccine neoantigens administered. Also, GEN-009 reportedly has proven to be unique among neoantigen vaccines in its ability to elicit ex vivo CD8+ T cell responses, which were observed for 47 percent of vaccine neoantigens.

The company believes that these data could represent a breakthrough in the development of neoantigen vaccines—using patients’ own T cells and antigen-presenting cells to select vaccine neoantigens results in higher immunogenicity, and Genocea is keen to explore whether this higher immunogenicity translates into greater clinical efficacy than seen with other neoantigen vaccines.

**IMAGING TUMORS MORE PRECISELY**

Taking a spin away from pharmacologic treatments toward surgery, but also with a nod toward cancer diagnostics, we have news from spring out of MIT that researchers there, working with surgeons and oncologists at Massachusetts General Hospital, have now developed a way to improve the accuracy of this debulking surgery for ovarian cancer.

Using a novel fluorescence imaging system, they were able to find and remove tumors as small as 0.3 millimeters—smaller than a poppy seed—during surgery in mice. Mice that underwent this type of image-guided surgery survived 40 percent longer than those who had tumors removed without the guided system.

“What’s nice about this system is that it allows for real-time information about the size, depth and distribution of tumors,” says Angela Belcher, the James Mason Crafts Professor of Biological Engineering and Materials Science at MIT, a member of the Koch Institute for Integrative Cancer Research and the recently appointed head of MIT’s Department of Biological Engineering.

The researchers are now seeking FDA approval for a Phase 1 clinical trial to test the imaging system in human patients. In the future, they hope to adapt the system for monitoring patients at risk for tumor recurrence and, eventually, for early diagnosis of ovarian cancer since the disease is often caught late when it is very hard to treat.

“A major focus for us right now is developing the technology to be able to diagnose ovarian cancer early, in stage 1 or stage 2, before the disease becomes disseminated,” Belcher comments. “That could have a huge impact on survival rates, because survival is related to the stage of detection.”

**CANCER RESEARCH NEWS**

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

July 2019 || DDNEWS 29
COMBINATION THERAPIES are nothing new, particularly when it comes to cancer treatment. Still, it is worth checking in on some of the more recent news on this front to see some of the new twists on an old approach, and to that end Roswell Park Comprehensive Cancer Center, MD Anderson Cancer Center and Synlogic Inc. all have some work to highlight.

IMMUNOTHERAPY-CHEMO COMBINATION GETS FDA APPROVAL

BUFFALO, N.Y.—A new cancer therapy based on the work of Dr. Ben Seon at Roswell Park has been approved by the U.S. Food and Drug Administration (FDA) for patients with an aggressive form of non-Hodgkin lymphoma. On June 10, the FDA granted accelerated approval to polatuzumab vedotin as part of a new chemotherapy/immunotherapy treatment combination for patients with relapsed or refractory diffuse large B-cell lymphoma.

Polatuzumab vedotin incorporates a monoclonal antibody—a manufactured protein that can bind to and kill tumor cells. While Roswell Park has played a role in many other FDA-approved innovations in cancer treatment and diagnostics, the approval of polatuzumab vedotin marks the first time an immunotherapy from Roswell Park has been part of an FDA-approved treatment.

Manufactured by Genentech Inc., polatuzumab vedotin is an antibody-drug conjugate that specifically targets CD30, a protein expressed in the majority of B cells. “What Ben has done is really remarkable,” said Dr. Kelvin Lee, the Jacobs Family Chair in Immunology and Senior Vice President for Basic Science at Roswell Park. “Through his systematic, diligent approach, he came up with ideas decades ago in his lab that larger teams have only begun to hit upon in the last few years.”

“I didn’t take the conventional approach. I decided to develop a new system for isolating antigens,” observed Seon, and he says he is especially proud that a therapy he developed has helped many patients at Roswell Park, one of the participating sites in the clinical trials incorporating polatuzumab vedotin.

“My father died from stomach cancer when I was a high school student, and my brother died of cancer many years ago in his 50s. So it’s always been in my mind that hopefully someday I could find a new cancer drug, a better cancer drug.”

TRIPLE COMBO SHOWS PROMISE AGAINST ADVANCED MELANOMA

HOUSTON—Combining two types of drugs that, separately, have extended the lives of people with metastatic melanoma has yielded higher response rates in three early-phase clinical trials reported in Nature Medicine, one led by MD Anderson Cancer Center investigator.

Patients received the immune checkpoint inhibitor vemurafenib and the MEK inhibitor cobimetinib.

About half of advanced-stage melanoma patients have the BRAF mutation in their tumors. The 71.8-percent response rate to the triple combination is similar to that of patients who receive vemurafenib and cobi metinib in the frontline setting. The durability of the triple combination is comparable to the greater durability seen with anti PD-L1/ PD-1 checkpoint blockade compared to that of the targeted therapy combination.

Research by MD Anderson and an Australian group of investigators found that treatment with BRAF inhibitors increased the penetration of immune T cells in tumors, providing a scientific basis for testing the combination.

Nature Medicine also published two other studies that used a different combination of drugs against the same targets (PD-1 inhibitor pembrolizumab plus BRAF inhibitor dabrafenib and MEK inhibitor trametinib) that reported similar results.

A SYNTHETIC BIOTIC IO PROGRAM

CAMBRIDGE, Mass.—This spring, clinical-stage drug discovery and development company Synlogic Inc. announced that preclinical data from its immuno-oncology (IO) program were featured in two presentations at the annual meeting of the American Association for Cancer Research (AACR). The data demonstrate that, in mouse models, Synlogic’s Synthetic Biotic medicines were shown to stimulate an antitumor response and robustly reprogram the tumor microenvironment, potentially enabling the treatment of a variety of cancers.

“Our IO program highlights the potential of our Synthetic Biotic platform for the design and engineering of novel living medicines with multiple mechanisms of action to treat a broad range of diseases, including cancer,” explained Dr. J.C. Gutiérrez-Ramos, Synlogic’s president and CEO. “Our approach enables us, in a single treatment, to locally deliver multiple, regulatable activities that stimulate an immune response and mobilize the immune system against the tumor and its metastases. We intend to advance our first IO program into IND-enabling studies this year.”

Synlogic is focused initially on developing Synthetic Biotic medicines to treat so-called “cold tumors,” which lack infiltrating antitumor T cells, by first stimulating an innate antitumor response to make the tumor “hot” and then modifying the tumor microenvironment (TME) to enable T cell expansion and the development of memory, using a single agent to both prime T cells to mount an immune response and sustain the response.

In a presentation in the late-breaking research immunology session, “Activation of Innate and Adaptive Immunity via Combinatorial Immunotherapy using Synthetic Biotic Medicines,” Synlogic described two new genetic circuits engineered into E. coli Nissle, an immune “initiator” STING activating circuit (SYN-STING) and an immune “sustainer” kynurenine consuming circuit (SYN-Kyn).

Among the findings were that combining SYN-Kyn with a checkpoint inhibitor led to profound antitumor activity in the CT26 immunocompetent tumor model and that a strain engineered to combine both genetic circuits (SYN-STING-Kyn) demonstrates equivalent production of c-di-AMP and consumption of kynurenine in vitro compared to the individual strains SYN-STING and SYN-Kyn, respectively.

The second presentation, “Metabolic Modulation of the Tumor Microenvironment using Synthetic Biotic Medicines,” demonstrated that engineered bacterial strains designed to consume either kynurenine (SYN-Kyn) or adenosine (SYN-Ade) effectively relieved TME immunosuppression and promoted antitumor activity. One of the findings was that a combination of either SYN-Kyn or SYN-Ade with checkpoint inhibition led to superior antitumor activity in the MC38 immunocompetent tumor model compared with checkpoint inhibitors alone. »
**BRIEFS**

**QIAstat-Dx hits the market**

GERMANTOWN, MD & HILDEN, Germany—The second quarter of 2019 saw the U.S. launch of QIA-GEN N.V.’s QIAstat-Dx syndromic testing system following 510(k) clearance by the FDA and the multiplex QIAstat-Dx Respiratory Panel for simultaneous qualitative detection and identification of multiple respiratory viral and bacterial pathogens. The company estimates that the respiratory infections space has an addressable market of roughly 1.5 million tests annually in the United States, and plans to launch a gastrointestinal panel as well later this year.

“QIAstat-Dx delivers the precision of molecular testing to identify hard-to-diagnose respiratory infections, which sicken millions of U.S. patients each year and kill tens of thousands. We are pleased to roll out the QIAstat-Dx Respiratory Panel for healthcare providers as they begin to prepare for the 2019-20 flu season,” said Thierry Bernard, QIAGEN’s senior vice president and head of molecular diagnostics.

**A good showing by Parsortix**

SURREY, U.K.—ANGLE plc’s clinical study of Parsortix in metastatic breast cancer delivered positive results, the company announced recently. The study was meant to support a de-novo submission to the FDA for Class II regulatory clearance for the Parsortix system, and successfully demonstrated the system’s ability to capture and harvest cancer cells from the blood of a significant proportion of metastatic breast cancer patients. In addition, the harvested cells were able to be interrogated via several analysis techniques and were viable for use in generating cDNA libraries of sufficient quality for mRNA-seq evaluation. ANGLE noted that additional experiments will be necessary to support the clearance, but the company still expects that it will be able to complete all studies and submit early in the fourth quarter of this year to enable FDA clearance in early 2020.

**A stool test for cirrhosis**

UC San Diego researchers analyze stool microbes to diagnose liver disease

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**DOUBLE DUTY FOR INGESTIBLE TECHNOLOGY**

Micro-bio-electronic device might be able to diagnose and treat GI problems

**By Kristen Smith**

SAN DIEGO—At the most recent Digestive Disease Week event, the biotech company Progenity presented promising results of studies into the utilization of ingestible technologies to monitor diagnose and treat gastrointestinal disorders. The ingestible micro-bio electronic device (IMBED) technology, sometimes referred to as an “intelligent pill,” is already transforming healthcare, attracting research and investment as it racks up 19-percent growth year over year, the company says.

In the simplest terms, IMBEDs are small devices made of biologically safe materials that can gather information about their environment, transmit data to a compatible receiver and potentially deposit precision doses of medicine exactly where it will be of most benefit. Subhra Pradhan, in her January article in PReScotur, describes IMBEDs like this: “They are ingestible electronic devices, roughly the size of a medicine capsule, composed of biocompatible materials that make up a power supply, microprocessor, controllers, sensors, etc., giving the device the ability to pre-communicate for use in the healthcare industry for disease diagnostics and monitoring.”

For Progenity, the company’s goal is to transform healthcare toward more precise and personal diagnostics and treatment. They saw a vast unmet need in the gastrointestinal space, both for a better assessment tool and for better therapies. According to Dr. Mitch-ell Lawrence Jones, vice president of translation and clinical development at Progenity, it is time to move beyond using drugs developed to treat other conditions for GI issues, and to move beyond the current threshold of 15-percent efficacy above placebos.

“We aim to improve GI diagnosis and treat-ment through internal diagnostic tests,” he says. “We think of our capsule as a ‘black box’ for the body, collecting biomarkers unique to that methodology that can’t be obtained from a blood sample or a fecal sample. Today, patients must go on a diagnostic odyssey [to understand symptoms], using scopes, ultrason-ounds, blood tests and more. None of these are adequate as the gold standard for GI conclusions.”

Progenity’s capsule, still in preclinical investigation in animal subjects, demon-strates the potential to self-locate and assess difficult-to-reach areas to monitor colorectal cancer, for example. The body expels the capsule through normal digestion, but only after collecting critical information. On the therapeutic side of the capsule’s utility, the IMBED can self-locate and place ingest **CONTINUED ON PAGE 33**
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Developing novel biomarkers allows physicians to specifically screen and diagnose patients, stage disease progression, monitor response to treatment, and improve the rigor and efficiency of clinical trials toward developing effective drugs for the prevention and treatment of the disease. “The diagnostics accelerator brings together philanthropic capital with a venture investment mindset to advance bold new ideas for easier and more accurate diagnosis of Alzheimer’s disease and related dementias,” Lauder says.

In a “Gate’s Notes” post published April 2, Gates wrote, “It’s hard to overstate how important finding a reliable, affordable and easy-to-use diagnostic is for stopping Alzheimer’s.” The use of advanced technology and digital tools, such as blood tests and mobile phone apps, can help empower doctors, patients and caregivers, ultimately leading to better outcomes.

Dr. Howard Fillit, ADDF founding executive director and chief science officer, reminds the interest from the philanthropic as well as the scientific community has been tremendous. The ADDF is excited to expand its research support for the development of digital biomarkers that will augment traditional lab tests and imaging tools with creative and cost-effective approaches to collect, track and analyze patient data. Over 100 drugs are currently in clinical trials aimed at slowing or preventing AD, but these drugs are targeting many of the currently known contributors of the disease including increased inflammation, epigenetic changes, vascular problems and changes in metabolism. “We anticipate that a combination of treatments will be needed,” Fillit says, adding that a precision medicine approach to AD will allow physicians to treat the specific pathways that contribute to each individual patient’s disease.

Digital tools could also allow the remote capture of changes in a patient’s physical and mental status at various stages of Alzheimer’s disease, and information gathered can span from cognitive assessments to motor ability to sleep disruptions.

“Real-world evidence has the potential to add significant value to clinical trials, increasing patient engagement, enhancing monitoring and greatly improving treatment outcomes,” Fillit points out. “In our first request for proposals, nearly 300 letters of intent proposing new diagnostic technologies may offer additional options for patients and also help our pharmaceutical partners accelerate their development efforts.”

Detecting cells and CD4 of interest from liquid biomarkers requires extremely specific, precise technology. As explained by Resolution Bioscience, “The circulating tumor DNA (ctDNA) may be less than 0.1 percent of all the ctDNA. Therefore, there may be a plenitude of potential targets in whole blood or ‘obscuring’ each meaningful signal. The fragments are all made of the same material: DNA. Therefore, it is harder than a needle in a haystack—you are actually looking for one slightly different needle in a large pile of needles.”

“The haploid human genome contains 3 billion bases. Some driving mutations are single nucleotide variations (SNVs), where a single base change has occurred. For example, an adenine (A) becomes a guanine (G). Some of the SNVs are heterozygous mutations, so instead of one in three billion, it’s actually a mutation of one in six billion bases. If trying to reach a detection limit of 0.1 percent of ctDNA in 99.9 percent background ctDNA, the problem becomes the ability to detect one molecule in six trillion bases.”

Resolution’s HRD assay, supported by its patented ctDNA NGS analysis platform, has been explored in a number of studies. With it, Resolution was the first company to demonstrate gene detection deletion in ctDNA in a small cell lung cancer study led by Vanderbilt University researchers, who found that ctDNA sequencing enables improved disease monitoring, treatment response monitoring and warning of relapse. In a publication by AstraZeneca, Resolution’s technology showed the highest positive predictive value and lowest false-positive rate of four leading NGS liquid biopsy companies in a blinded comparison study.

“In the topic of leading liquid biopsy contenders, Canacced Genuity diagnostics analyst Mark Massaro wrote in a note to investors that Guardant Health (GH), Natera and Illumina are all companies to keep an eye on within this space. He expects growth for the space as a whole—as well—particularly in determining treatment options for patients with advanced cancer, as well as in recurrence monitoring and minimal residual disease detection. Massaro also noted that Canacced Genuity expects to see liquid biopsy testing begin to replace tumor profiling. A recent MEDACorp specialist call hosted by SVB Leerink LLC looked at liquid biopsy within the gastrointestinal field, and also touched on Guardant Health as a player to keep an eye on, calling the company a ‘best-in-class liquid biopsy opportunity in a massive high-growth market.’ Leerink noted that call participants felt that ‘Recurrent or residual disease monitoring opportunity remains most promising for [GH] and its LUNAR assay—with potential to reduce adjuvant trial size significantly and improve patient selection—making it, in our view, highly attractive for biopharma and for commercial post-surgical treatment testing.” However, both participants agreed that Guardant Health data for LUNAR seemed to be more promising in colorectal cancer screening market.

The participating oncologist said that “GH’s recent data on the LUNAR LBS assay holds the most promise in recurrence monitoring and adjuvant therapy trials. The Oncologist expects that LUNAR can help reduce trial size, cost and turnaround time for adjuvant therapy by 80 percent in certain cases—only selecting those patients that are most likely to relapse—an attractive proposition for biopharma.”

The recurrence market especially has significant potential, with Guardant estimating that the overall recurrence monitoring market for all cancers is $15 billion.

EDITCONNECT: E071923

The inaugural Diagnostics Accelerator award winners are, from left to right: Drs. Kaj Blennow, Peter van Wijngaarden, Tom MacGillivray and Salilha Moussaoui. Diagnostics SAS, France, was awarded $488,997 for a study employing a novel combination of retinal biomarkers capturing neurodegeneration and vasculature dysfunction often found in Alzheimer’s disease with advanced imaging analyses. Dr. Peter van Wijngaarden of the Centre for Eye Research Australia was awarded $420,321 for a study to test a simplified eye scan, which can detect amyloid in the retina prior to signs of cognitive decline. The team is developing a more portable and inexpensive prototype camera to establish whether this novel eye imaging technique could replace expensive PET imaging or invasive CSF tests for Alzheimer’s diagnosis and detect early signs of AD prior to signs of cognitive decline.

“Our overarching goal is to develop drugs for the treatment and prevention of Alzheimer’s,” Fillit says. “Because Alzheimer’s is a disease of aging and old age, delaying the onset by just five years would reduce the number of cases by 50 percent. Acceleration of biomarkers is already enabling the beginnings of a precision medicine approach to Alzheimer’s.”
A very specific dose of the right drug to the exact spot where it will be most efficacious. This topical application directly to the stomach, as a liquid soluble drug, reportedly maximizes bioavailability compared to a metabolized dose, which can cause systemic toxicity. It can deliver to the surface of the mucosa of the bowel, which limits systemic exposure and curtails the immune-suppressant action of some drugs that can be dangerous at the wrong metabolized dose.

In addition, it allows for precise dose rationale and for multiple drugs to be delivered in synergistic dosing. The hope at Progenity is that eventually their capsule will be able to deliver precision dosing, but also combination therapy to the exact location to incur benefit.

Progenity is working in conjunction with the FDA, receiving critical advice and assistance in preparing for early human trials. They expect to submit an Investigational New Drug application soon and will proceed along the regulatory pathway, submitting biologics and exploring options as an innovator, or approval on the platform itself. They are also exploring the development and manufacture of the very drugs that the capsule can deliver.

“These platelet technologies are intended to directly address challenges clinicians face in diagnosing gastrointestinal disorders and treating patients with therapies that can result in low response rates and high toxicity,” stated Harry Stylli, CEO, chairman and a co-founder of Progenity. “Our proof-of-concept studies demonstrate great promise that these technologies can be used in a variety of applications to greatly improve the ability of clinicians to diagnose, treat and monitor digestive diseases. Progenity is also developing and manufacturing its own pipeline of drugs with established efficacy and safety profiles in IBD. We believe our proprietary platform will help improve the therapeutic safety and efficacy of currently available therapies and their combinations for the treatment of IBD and other diseases.”

IMBEDs are already in use in fascinating ways. Australian scientists have demonstrated the first pilot human trial on gut gas-sensing digital pills, providing some powerful new insights into gut activity which could revolutionize our understanding of the gut, gastrointestinal biomolecules, food retention time, digestion, food absorption or lack thereof, microbiome composition and much more, all in real time and in a noninvasive manner. Other companies are using IMBEDs to monitor drug compliance, alerting doctors or caregivers when someone has neglected to take their medication or when they might be at risk for an overdose. Also, an Israeli company is testing an IMBED instead of having an invasive colonoscopy.

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Charles River cultivates change

Charles River constructs new collaborative science partnerships

BY MEL J YATES
WILMINGTON, Mass.—SVB Leerink analysts have noticed that Charles River Laboratories (CRL) has been busy with recent deals lately, pointing out that “in 2014 CRL has entered into ~15 different M&A transactions, according to FactSet. This includes 14 acquisitions and one asset sale ranging from ~$2.3M to $800M. During this time, CRL has acquired ~5 companies for ~$200M+ including Galapagos NV/CRO, Celsis International, WIL Research Laboratories, MPI Research Inc. and Citoxlab France SAS.”

“In May, one of Charles River’s partners, Dogma Therapeutics, discovered orally bioavailable small-molecule PCSK9 inhibitors that could hold promise for patients suffering from hypercholesterolemia and cardiovascular disease. Market watchers also see a lot of potential for Charles River’s future in the preclinical space. “We like how CRL’s preclinical focus allows the company to begin relationships with customers early on in the drug development process. Through their solutions, CRL is able to provide the necessary equipment and services to their customers to give them the best odds of success,” Leerink analysts said. “The drug development market is fast-growing, with the preclinical market experiencing more rapid growth than other segments of the industry. Our MEDACorp checks on CRL have consistently come back positive, with specialists describing CRL as the ‘Cadillac’ of preclinical trials.”

In May, one of Charles River’s partners, Dogma Therapeutics, discovered orally bioavailable small-molecule PCSK9 inhibitors that, when administered to dyslipidemic large animals, were found to elicit significant and robust lowering of LDL cholesterol following multiple weeks of oral dosing. The breakthrough holds great promise for patients suffering from hypercholesterolemia and cardiovascular disease. “Our team is extremely proud to have worked closely with Dogma throughout the development of its oral PCSK9 inhibitor,” stated Birgit Ginrich, corporate executive vice president of global discovery and safety assessment for Charles River.

Several antibody-based inhibitors emerged following the rapid accreditation of the PCSK9 therapy, vaccinations and more, according to the company. Phase 1 construction is slated to start in August. When the campus is completed, the company’s annual capacity will exceed $1 billion in biologics. The first two-story building will increase GMP and GMP-Source production capacity by as much as 10 times its current output. Aldevron’s 189,000-square-foot addition, which will connect to the existing GMP facility, is expected to be fully operational by the first quarter of 2021. Three new buildings will be built over the next three to five years to support the rapidly growing field of genetic medicine. The company’s plans include Aldevron CONTINUED ON PAGE 35.

MARKING AN ANNIVERSARY

BioAscent records successful first year as fully integrated discovery services CRO

BY DONNEWS STAFF
NEWHOUSE, U.K.—BioAscent Discovery Ltd. recently announced a threefold increase in revenues during 2018, with projections on-track for a further 2.5-fold increase in 2019. These significant results have been driven, the company says, by substantial contract wins for both BioAscent’s established compound management services and its newer integrated drug discovery offering.

In addition to this commercial revenue, the company has recently secured a second, five-year contract as part of the European Lead Factory’s ESCulab Project, to provide the storage and management of more than 500,000 compounds, as well as biological hit characterization.

Following investment last year and expansion to become an integrated discovery services contract research organization (CRO), BioAscent now supports an international cus...
contract services

ALDEVRON

Adding 20,000 square feet of quality control and product storage space to Aldevron's current 70,000-square-foot GMP and GMP-Source manufacturing building, the world's largest plasmid DNA manufacturing facility, which opened in September 2018. The next addition will be an 89,000-square-foot, two-story administration and client visit center, connected to the manufacturing space by skyway. The last building will be a 96,000-square-foot research and development, technical operations, and training center. Upon completion, the total square footage will be nearly 500,000 square feet, and the facility will be able to employ 700 people.

According to Michael Chambers, CEO of Aldevron, “This plan is designed to serve the biopharmaceutical industry with the world’s most advanced manufacturing platforms for gene and cell therapy. It is an honor for us to provide plasmids, gene editing enzymes and other biologics to support clinical and commercial applications that our clients are pioneering. The new campus will also enable large-scale production of novel products like nanoplastmids and micrinicles. Our mission has remained unchanged in 21 years to help our clients improve lives through innovative partnerships and scientific excellence. This campus has been, and will continue to be, designed to serve our current and future breakthroughs.”

Henry Hebel, chief operating officer of Aldevron, added, “Our industry is growing exponentially. We are building a campus to meet client demand, create a functional and inspiring environment for our staff and take us to the next level. Our robust expansion plan was designed by listening to and engaging with regulatory agencies, industry professionals and, most importantly, our clients. The design decisions promote efficiency and scaling, and the next generation of manufacturing optimization.”

In other news, Aldevron announced the appointment of Brian Walters as president of its antibody business unit and Tom Foti as president of its protein business unit. Walters, who currently serves as chief business officer at Aldevron’s headquarters, Foti, who currently serves as the vice president and general manager of Aldevron’s Madison, Wis., facility, will stay at that location. Both Foti and Walters will continue to report to Chambers and will help the company with strategic initiatives to expand and improve client support for gene and cell therapy research.

BioAscent

BioAscent’s results, explained Dr. Phil Jones, the company’s chief scientific officer. He notes that, “From the start, we prepared the ground for our commercial success by recruiting not just more people—we have four times the resource than at the start of last year and envisage ending the year with around 40 staff—but importantly, the best people. We’ve integrated highly experienced chemistry and biology teams who have significant track records of drug discovery success, and continue to build the team with high-caliber and well-respected scientists to meet the growing demand for our services.”

BioAscent is expanding to support the rapidly growing field of genetic medicine.

change

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target through human genetics. But despite large outcome trials showing a 15 to 20 percent reduction in cardiac events, the cost-effectiveness and wide use of antibody-based PCSK9i injectables has been questioned. Alternate approaches to PCSK9i inhibition were stymied by the expansive binding surface targeted by the antibodies. To date, only indirect approaches to PCSK9i inhibition by small molecules have been reported.

“It was an exceptionally rewarding experience for our team to have a close partnership with Dogma and Charles River as we rapidly advanced the program towards clinical study,” added Dr. Zhixiong Ye, chief scientific officer at Viva Biotech. “An orally-bioavailable small-molecule PCSK9i inhibitor will greatly impact the unmet medical needs of cardiovascular patients.”

The discovery is the result of close collaboration between Dogma, Charles River’s drug discovery team and Viva Biotech, proving the usefulness of partnerships. The combined team overcame the challenges of PCSK9’s expansive binding surface by finding small-molecule inhibitors that directly bind to a novel, cryptic binding pocket in PCSK9.

“We are excited to progress our first-generation oral PCSK9 inhibitor into the clinic to understand the potential for LDL lowering with our approach,” said Dogma Therapeutics co-founder Dr. Brian Hubbard. “Human data with our oral PCSK9i inhibitor will provide valuable feedback for ongoing research and catalyze our ability to deliver this important modality to more patients.”

Charles River also recently announced an investment in Resero Analytics, a software company providing data solutions to the biopharmaceutical industry, as was reported in the June edition of DDNews. Charles River plans to collaborate with Resero Analytics, and is now the exclusive contract research organization partner for TurboTox, a report-generating tool enabling faster delivery of high-quality reports.

“CRL is the market leader in Research Models and Services and will benefit from an increased number of drugs in the pipeline among global pharmaceutical and biotech companies,” Leerink analysts mentioned. “CRL’s end-market offers some of the highest margins in the healthcare industry, with a smaller partial contributor to the strong growth in active R&D pipelines globally. Since 2015, the number of drugs in preclinical development increased at a CAGR of ~9.5%, which we estimate is ahead of the clinical trial space (~5.8% CAGR for Phases 1-3).”

BioAscent continues from page 34

adding 20,000 square feet of quality control and product storage space to Aldevron’s current 70,000-square-foot GMP and GMP-Source manufacturing building, the world’s largest plasmid DNA manufacturing facility, which opened in September 2018. The next addition will be a 96,000-square-foot research and development, technical operations, and training center. Upon completion, the total square footage will be nearly 500,000 square feet, and the facility will be able to employ 700 people.

According to Michael Chambers, CEO of Aldevron, “This plan is designed to serve the biopharmaceutical industry with the world’s most advanced manufacturing platforms for gene and cell therapy. It is an honor for us to provide plasmids, gene editing enzymes and other biologics to support clinical and commercial applications that our clients are pioneering. The new campus will also enable large-scale production of novel products like nanoplastmids and micrinicles. Our mission has remained unchanged in 21 years to help our clients improve lives through innovative partnerships and scientific excellence. This campus has been, and will continue to be, designed to serve our current and future breakthroughs.”

Henry Hebel, chief operating officer of Aldevron, added, “Our industry is growing exponentially. We are building a campus to meet client demand, create a functional and inspiring environment for our staff and take us to the next level. Our robust expansion plan was designed by listening to and engaging with regulatory agencies, industry professionals and, most importantly, our clients. The design decisions promote efficiency and scaling, and the next generation of manufacturing optimization.”

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

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HALLE (SALLE), Germany—June 11 saw the official switch of Prehring AG’s company name to Vivoryon Therapeutics AG. The company will continue its focus on finding therapeutic solutions for Alzheimer’s disease, and PrB12, its lead molecule, will be moving into two clinical Phase 2b trials in Europe and the United States for the treatment of Alzheimer’s disease.

“Vivoryon, composed of ‘Vivid Memory On,’ expresses our strong commitment to develop a transformational therapeutic option for patients with Alzheimer’s disease against the backdrop of multiple late-stage industry disappointments. With our proprietary glutaminyl cyclase inhibition platform, we are technology leaders in this field which has also opened new opportunities to bring scientific excellence for the benefit of patients to other indications, as we currently see in immuno-oncology,” said Dr. Ulrich Dauer, CEO of Vivoryon Therapeutics.

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Advancing biologics

FDA takes new step to help advance the transition of certain biological products

BY DDNEWS STAFF

SILVER SPRING, Md.—In late June, the U.S. Food and Drug Administration (FDA) issued a proposed rule to amend its regulations on the use of master files for biological products. The proposed rule, if finalized, would allow certain applications for biological products approved under the Federal, Food, Drug, and Cosmetic Act to continue incorporating by reference information on drug substances, drug substance intermediates or drug products contained in drug master files (DMF) after the approved applications for those products are deemed to be licenses under the Public Health Service Act (PHS Act) on March 23, 2020.

The proposed rule would also codify the FDA’s existing practice that an application for a biological product under the PHS Act may rely on a master file, except for information on drug substances (active pharmaceutical ingredient, or API), drug substance intermediates (a material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API) or drug products (finished dosage forms, such as tablets or capsules).

In addition, the proposed rule would codify the FDA’s existing practice that information from a master file, including drug substance, drug substance intermediate or drug product information, may be relied on at the investigational phase of development for a product subject to licensure under the PHS Act.

Some of the applications (approximately 17, such as reproductive hormones and enzymes) that will be transitioned currently incorporate reference information contained in DMFs to support their application and were approved by the FDA based in part on the drug substance, drug substance intermediate or drug product information contained in those DMFs.

As the FDA says, “Many of these products have been marketed for decades and over this period, none of these products have been withdrawn or removed from the market for reasons of safety or effectiveness. For these products, the FDA has no reason to believe that the March 23, 2020, transition in and of itself introduces new risks to product safety, purity and potency.”

Additionally, after the transition, a proposed biosimilar and/or interchangeable product to one of these transitioned biologicals may not reference the DMF for the drug substances, drug substance intermediates or drug products information, consistent with existing practice for biological products submitted in Biologics License Applications and the use of master files.

AbbVie makes $63B play for Allergan

Proposed acquisition is said to be a ‘tranzformative’ move for both companies

BY JEFFREY BOULEY

NORTH CHICAGO, Ill. & DUBLIN—June 25 came with an announcement that caught market-watchers a bit by surprise: The news that AbbVie (ticker symbol ABBV) planned to acquire Allergan (ticker symbol AGN) for about $63 billion.

As analysts from SVB Leerink LLC noted the day of the announcement, “This morning’s announcement of the purchase of Allergan by AbbVie comes as a surprise, but is consistent with AbbVie’s intention to diversify away from their dependence on Allergan.”

AbbVie (pictured here) plans to diversify its pipeline markedly as well as grow the company size considerably by acquiring Allergan for about $63 billion.
**ALLERGAN CONTINUED FROM PAGE 36**

Humira. The transaction takes advantage of AbbVie’s dividend yield, discounted multiple and low borrowing cost, and significantly reduces their future dependence on their immunology franchise. With synergies, the combined company is likely to be able to maintain AbbVie’s impressive track record of dividend growth.

The deal news arrived even as speculation was percolating that Allergan might break up the company, splitting off its Botox franchise from the rest of the pharmaceuti
cal division, with Wells Fargo analyst David Maris adding, “This is a good opportunity for Allergan vs. the current share price.”

Also, Canaccord Genuity analyst Sumant Kulkarni wrote, “We see the overarching rationale for the proposed acquisition as a means to diversify AbbVie’s revenue base away from Humira, which is currently the world’s largest-selling therapeutic, and is facing biosimilar competition in the US in 2023. After having covered Allergan over several years in its various incarnations, we can see how [shareholders] may have a mixed response depending on their cost basis.”

For example, Kulkarni noted that three years ago, Pfizer failed to acquire Allergan when the U.S. Treasury Department scuttled the “tax inversion” deal, then added, “From where we sit today, however, our bottom line take is that we are encouraged by the focus that AbbV has placed on AGN’s neurology/ psychiatry assets.”

As AbbVie notes in its own words about its proposed deal with Allergan, the combina
tion will provide immediate scale and profitability to AbbVie’s growth platform, excluding Humira, significantly expanding and diversifying its revenue base with new therapeutic areas, including Allergan’s lead
ing medical aesthetics business.

Also, the deal is expected to:

- Enhance long-term R&D funding capacity, allowing for continued investment and sustained focus on innovative science and advancement of an industry-leading pipeline.
- Increase global commercial scale to further maximize the value of AbbVie’s attrac
tive portfolio of fast-growing products.
- Produce robust cash flow to support continued dividend growth, further investment in the pipeline and reduc
tion of debt levels.

Assuming all goes well with the deal with regard to shareholders and regulators, it is expected to close in early 2020.

“This is a transformational transaction for both companies and achieves unique and complementary strategic objectives,” said Richard A. Gonzalez, chairman and CEO of AbbVie. “The combination of AbbVie and Allergan increases our ability to continue to deliver on our mission to patients and shareholders. With our enhanced growth platform to fuel industry-leading growth, this strategy allows us to diversify AbbVie’s business while sustaining our focus on innovative science and the advancement of our industry-leading pipeline well into the future.”

Richard A. Gonzalez, CEO of AbbVie streams to secure long-term growth.”

But there is an unexpected aspect to this deal, Musciacco said, noting that “AbbVie
has turned to a rather diversified company, therefore the deal is expected to transform the
company’s portfolio. Importantly, the deal will also lower its reliance on Humira, meaning that just 41 percent of the combined company’s sales would be generated by this drug.

“AbbVie has a broad offering: roughly 50 percent of its sales are generated by
neurology drugs. That said, it also has drugs for ophthalmology, gastrointestinal, women’s health and cardiovascular indications, just to name a few. Its sole blockbuster brand is Botox, which—similarly to Humira—has been approved in multiple indications. Notably, Allergan also has several promising pipeline assets that will contribute to future sales growth; for example, ubrogepant and atogepant are two oral calcitonin gene-related peptide receptor antagonists in late-stage development for the lucrative migraine market.”

Musciacco also expects that regulators are fairly likely to require that the companies
divest some of their assets. 

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NEW MASS SPEC FOR THERMO
Thermo Fisher Scientific acquires Slovakian mass spec software firm HighChem

BY DDNEWS STAFF
SAN JOSE, Calif.—In June, Thermo Fisher Scientific acquired HighChem, a developer of mass spectrometry software based in Bratislava, Slovakia. Financial and other terms of the transaction were not disclosed. The company provides software that is used by pharmaceutical and metabolomics laboratories for analyzing complex data and identifying small molecules. “Our customers rely on us to provide advanced software solutions that interpret data quickly and accurately to make compound identification simple and understandable,” said Mitch Kennedy, president of chromatography and mass spectrometry at Thermo Fisher Scientific. “The addition of HighChem’s software solutions to our existing mass spectrometry software portfolio will enable us to deliver greater value for our mass spectrometry customers.” HighChem will be integrated into Thermo Fisher’s chromatography and mass spectrometry business, which is part of the firm’s Analytical Instruments unit.

As a leading provider of life-sciences technology globally, Thermo Fisher Scientific works to help customers accelerate research, solve complex analytical challenges, improve patient diagnostics, deliver medicines to market and increase laboratory productivity. Its premier brands include Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific and Unity Lab Services.

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DURHAM, N.C.—A study released recently in STEM CELLS Translational Medicine reportedly demonstrates how preconditioning mesenchymal stem cells (MSCs) enhances their ability to treat acute respiratory distress syndrome (ARDS), which could point to a way of developing more effective MSC treatments for clinical application, according to Dr. Ben Antebi, who led the team of investigators from the U.S. Army Institute of Surgical Research and Stanford University.

ARDS, a life-threatening condition in which fluid accumulates in the lungs, has a mortality rate of up to 46 percent. Although the many causes include pneumonia, sepsis and drug overdose, the majority of ARDS cases are due to burn injuries, especially those involving smoke inhalation—thus the interest from the military, as it is a significant complication in combat casualty care.

While no drug has proven effective in treating ARDS, studies have shown that treatment with MSCs collected from bone marrow improves fluid clearance in the lungs and decreases their permeability, while also combating infection and inflammation. Researchers believe this is due to a key feature of ARDS: an imbalance between pro- and anti-inflammatory mediators in the body known as cytokines. MSCs are known to balance key inflammatory cytokines (TNF-α, IL-1, IL-6, IL-10) and secrete lipid compounds, as well as mets of other immune cells.

According to the research, though, a major drawback to this potential therapy is the fate of the MSCs following exposure to a hostile microenvironment, such as in ARDS. One proposed solution is to “recondition” the MSCs prior to treatment in serum coming from subjects with ARDS.

The study looked at how that might work. In its first phase, a group of pigs suffering from ARDS (due to smoke inhalation and burns) were treated with MSCs. A group of uninjured, untreated pigs and another group comprised of untreated ARDS-injured pigs were used as controls. In the second phase, serum was collected from the three groups of pigs to “recondition” the pigs’ MSCs ex vivo. In the study’s third and final phase, the methods were repeated using human MSCs and lipopolysaccharide, which induces inflammation-like ARDS in vitro.

When each group of animals was analyzed for expression of the inflammatory mediators, Phase 2 results showed that allogeneic MSC treatment was able to regulate the ARDS symptoms. Interestingly, outcomes from Phase 2 showed that preconditioning MSCs with serum from subjects with untreated ARDS had a negative impact on how the cells functioned, while conversely, Antebi reported, “We found that MSCs reconditioned with serum previously exposed to MSCs enhanced their regenerative function. In addition to the known paracrine function of MSCs, we demonstrate that MSCs stimulate themselves via autocrine mechanisms. This leads us to conclude that this ‘pre-exposure’ technique can be used to augment MSC function for use in clinical applications in treating ARDS.”

Spero announces collaboration to develop SPR720 for tuberculosis

CAMBRIDGE, Mass.—Spero Therapeutics Inc, a multi-asset clinical-stage biopharmaceutical company focused on identifying, developing and commercializing treatments in high unmet need areas involving multi-drug resistant bacterial infections and rare diseases, has announced a collaboration with the Bill & Melinda Gates Medical Research Institute (Gates MRI) to develop SPR720 for the treatment of lung infections caused by Mycobacterium tuberculosis, an indication that is designated as a critical concern by the World Health Organization.

SPR720 is an orally administered antimicrobial agent currently being developed by Spero Therapeutics for the treatment of rare non-tuberculous mycobacterial (NTM) infections. Spero has granted Gates MRI an exclusive license to develop, manufacture and commercialize SPR720 for the treatment of tuberculosis (TB) in low- and middle-income countries.

Gates MRI will conduct and fund preclinical and clinical studies for the development of SPR720 against TB, and also fund certain collaborative activities in furtherance of Gates MRI’s charitable purposes. SPR720 was discovered by Vertex Pharmaceuticals and was acquired by Spero Therapeutics in 2016.

“We are excited about the prospects of SPR720 for treatment of NTM, and also see an important unmet need in the treatment of TB around the world,” said Dr. Ankur Mahadevia, CEO of Spero Therapeutics. “Spero will benefit from the significant development and industry experience that the Gates MRI team can offer, as well as synergies between the TB and NTM development paths as SPR720 progresses through clinical trials.”

SPR720 is currently being evaluated in a double-blind, placebo-controlled Phase 1 clinical trial to assess the safety, tolerability and pharmacokinetics of SPR720 in healthy volunteers. Spero Therapeutics expects to report top-line data from the Phase 1 clinical trial in the second half of 2019. Preclinical in-vitro and in-vivo studies have demonstrated the potency of SPR720 against clinically important mycobacteria. ©
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Mark Wigglesworth, Director of High-Throughput Screening, AstraZeneca, United Kingdom

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