Meeting a new mechanism

Samumed publishes unique mechanism of action for SM08502
BY MEL J. YEATES
SAN DIEGO—In late 2019, Samumed LLC noted the publication of data demonstrating a novel mechanism of action for SM08502 in preclinical gastrointestinal cancer models. The article, entitled “The CLK inhibitor SM08502 induces anti-tumor activity and reduces Wnt pathway gene expression in gastrointestinal cancer models,” was published in the journal Cancer Letters.

“SM08502 is a CDC-like kinase (CLK) inhibitor and … a potent inhibitor of CLK2 and CLK3. This publication shows that both CLK2 and CLK3 are oncogenic kinases, meaning they help to drive the formation of cancer through the activation of key pathways, including, as Samumed discovered, the Wnt signaling pathway,” says Dr. Yusuf Yazici, chief medical officer of Samumed. “Through this CLK inhibition, SM08502 can reduce Wnt pathway activity, which is aberrantly activated in 90 percent of colorectal cancers. More specifically, these data show that SM08502’s Wnt pathway inhibition occurs via the disruption of alternate splicing of key Wnt-related genes, resulting in their reduced expression.”

Collaboration “DUBbed” a success
MISSION AND AbbVIE DEAL REACHES MILESTONE AS PARTNERSHIP CONTINUES
BY KELSEY KAUSTINEN
CAMBRIDGE, U.K.—A collaboration that began in November 2018 between Mission Therapeutics and AbbVie has reached its first significant milestone with the identification of several deubiquitylating enzymes (DUBs) as potential drug targets. AbbVie has selected a panel of DUBs that will be advanced into further characterization and screening activities.

The collaboration is focused on the identification of specific DUBs and inhibitor compounds as potential treatments for Alzheimer’s disease and Parkinson’s disease. The agreement gives AbbVie the option to continue further development.

Phase 3 on the horizon
ORMED’S ORAL INSULIN CANDIDATE SHOWS EFFICACY IN PHASE 2B DIABETES TRIAL
BY KELSEY KAUSTINEN
NEW YORK—An estimated 30 million people in the United States currently have diabetes, nearly 10 percent of the country’s total population. Worldwide, the total number was 422 million in 2014, according to the World Health Organization, with an estimated 1.6 million deaths attributed to diabetes in 2016. As Western diets and lifestyle impacts lead to rising incidence, and as injectable insulin costs continue to skyrocket, an oral insulin option has become a common goal to make disease management easier for diabetic patients.

One of the frontrunners in the race for the first oral insulin drug is Oramed Pharmaceuticals Inc., which announced in Q4 2019 that it had positive data from the first cohort of its Phase 2b trial of ORM-0801, which is assessing the safety and efficacy of the oral insulin candidate in patients with type 2 diabetes and inadequate glycemic control on oral antihyperglycemic agents.

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Mission Therapeutics and AbbVie have reached the first key milestone in a collaboration to discover therapeutics to treat Alzheimer’s disease and Parkinson’s disease. Pictured here is AbbVie’s research center in North Chicago.

Mission Therapeutics and AbbVie have reached the first key milestone in a collaboration to discover therapeutics to treat Alzheimer’s disease and Parkinson’s disease. Pictured here is AbbVie’s research center in North Chicago.
CVD tech market to pass $40B by 2030

BOSTON—In its latest report, “Cardiovascular Disease 2020-2030: Trends, Technologies & Outlook,” IDTechEx Research forecasts that the cardiovascular disease (CVD) technology market will exceed $40 billion by 2030. The company notes, “As developers’ understanding of this disease grows, so will the range of devices at their disposal to address it. They have only scratched the surface of how technology can improve CVD patients’ lives and, as they dig deeper, they will continue to unlock the potential of this growing market.”

Although CVD has been a major health concern for decades, researchers are still struggling to address it or even understand it. Much of the problem lies in the disease at every stage of progression. Technology is helping to improve the way CVD can be detected, monitored and treated. Diagnosing CVD is the first step in patients’ road to recovery. It is imperative to detect the disease early in order to administer treatment while it is still treatable. In addition, preventing the disease altogether is becoming more important in healthcare. The main approaches for detecting CVD are currently in-vitro diagnostics at point-of-care (POC) and the use of artificial intelligence (AI) in cardiovascular imaging. AI in imaging is of particular interest being in general, because it is the integration of AI into these systems that is truly innovative. The four main types of POC diagnostics technologies are lab-on-a-chip, electrochemical test strips, lateral flow assays and molecular diagnostics.

Remote patient monitoring (RPM), which enables the patients’ health to be examined from a distance, is rising in prominence. Cardiovascular RPM involves a number of connected medical devices for use in the home. Wearables—such as skin patches, accessories and smart clothing—are particularly relevant, as most innovations are made in this field. Many forms of CVD are chronic in nature, meaning that they worsen over time. Thus, once the disease has been diagnosed it is imperative to initiate treatment as soon as possible in order to provide positive patient outcomes. Current trends in the treatment of CVD revolve around cardiac rhythm management and cardiovascular tissue generation. The technologies are in various stages of development—some have been commercially available for decades and others are still in the proof-of-concept phase. The differences in levels of development reflect the depth of researchers’ understanding of the diseases in question. For instance, pacemakers have been in use for over 50 years, as cardiac rhythm was one of the first areas of cardiovascular health to be investigated. On the other hand, cardiac tissue engineering and bioprinting technologies are still in their infancy due to a lack of understanding of the complexities of recreating human tissue.

Although CVD has been a major health concern for decades, researchers are still struggling to address it or even understand it. Much of the problem lies in the disease at every stage of progression. Technology is helping to improve the way CVD can be detected, monitored and treated. Diagnosing CVD is the first step in patients’ road to recovery. It is imperative to detect the disease early in order to administer treatment while it is still treatable. In addition, preventing the disease altogether is becoming more important in healthcare. The main approaches for detecting CVD are currently in-vitro diagnostics at point-of-care (POC) and the use of artificial intelligence (AI) in cardiovascular imaging. AI in imaging is of particular interest being in general, because it is the integration of AI into these systems that is truly innovative. The four main types of POC diagnostics technologies are lab-on-a-chip, electrochemical test strips, lateral flow assays and molecular diagnostics.

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ALTERNATIVE COAGULATION PROMOTERS AND GENE THERAPIES GRADUALLY DRIVE HEMOPHILIA MARKET

LONDON—According to data and analytics company GlobalData, the hemophilia A and hemophilia B market is poised to increase from $6.93 billion in 2018 to $9.29 billion in 2028 for a modest compound annual growth rate (CAGR) of 3 percent.

Replacement factors are the current standard of care, representing 97 percent of the total sales of the hemophilia market in 2018. However, their market share is expected to decline to 70 percent by 2028 due to the introduction of alternative coagulation promoters (ACPs) and gene therapies, which promise to target significant areas of unmet need such as reducing the burden of intravenous infusions and reducing the risk of developing neutralizing antibodies, or inhibitors, against replacement therapies.

“ACPs and gene therapies are the most anticipated drug classes for the treatment of hemophilia A and B, as they will provide more effective treatments for patients with inhibitors, more convenient administration routes and less-frequent dosing, and, in the case of gene therapies, provide a potential cure for the disease.”

Dr. Tajekesa Chapman of GlobalData

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HCS market to see CAGR of just under 10 percent

DUBLIN—Per the recent report available from Research & Markets and titled “High Content Screening Market—Growth, Trends, and Forecast (2019-2024),” the high content screening (HCS) market was valued at around $660 million at the beginning of the five-year forecast period, and is expected to reach a market value of approximately $1.05 billion by the end of it, for a compound annual growth rate of 9.8 percent.

As the report notes, under the conventional method of toxicity studies, large libraries are screened in search of potential drug candidates. This method is expensive, resource- and time-consuming, and has a low success rate. Consequently, HCS solutions for testing the potential toxicity of chemicals and complex substances are being adopted by pharmaceutical companies to improve in-vitro toxicity testing by reducing the time and cost.

The need for cost containment in pharmaceutical R&D, advancements in informatics solutions and imaging instruments, and government funding and venture capital investments across developed markets are the major factors driving the growth of the HCS market.
Making waves with macrophages

NTU Singapore scientists discover new key to promote insulin production in pre-diabetes patients

BY LORI LESKO

SINGAPORE—With obesity on the rise worldwide, Nanyang Technological University (NTU) scientists have discovered that a type of immune cell known as “pancreatic islet macrophage” is capable of promoting insulin production during the pre-diabetes phase, before the full-blown disease takes hold. The NTU team’s findings are published in the peer-reviewed journal American Journal of Physiology–Endocrinology and Metabolism, and supported by the Singapore Eye Research Institute, which provided the advanced imaging equipment for the research.

Although macrophages were not previously known to produce or regulate insulin, and had often been overlooked in diabetes research, the NTU team believed that the macrophages could be harnessed through new targeted treatments to help prevent type 2 pre-diabetic patients from suffering the physical complications and medical expenses of becoming fully diabetic.

Working with an international team of scientists, a five-year study was led by Yusuf Ali, assistant professor of metabolic disease molecular and cellular dysfunction from NTU’s Lee Kong Chian School of Medicine. “There are currently more than 300,000 people in Singapore—and many more around the world—living and coping with type 2 diabetes,” Ali says. “However, even more people are living in the pre-diabetes phase. And if we could detect it early, it would be much easier to reverse any negative progression of the condition.”

Located in various organs such as the heart, lungs and liver, macrophages are large, with a diameter of approximately 15 micrometers. They consume and clear debris and pathogens, often referred to as “garbage collectors,” but can also be harmful when unleashed in excess.

In an effort to harness the macrophages’ potential, the team discovered the macrophages’ unique ability to control insulin production in the islets of healthy rats.

In diabetes, insulin production drops, and the body can’t respond properly to blood sugar levels. The NTU team investigated the potential of macrophages to regulate insulin production (previously believed to be under the control of beta cells), and found that NTU’s LEPI cells (LEPI represents retinal pigment epithelial, and is short for LEP) can be made to produce insulin.

“Analyses of the LEPI cells’ insulin production before and after macrophage treatment revealed that the macrophages were making an active and significant contribution to the insulin production,” Ali said.

The NTU scientists then tested the LEPI cells in diabetic rats, and found that the LEPI cells maintained their insulin-producing abilities even after the injection of macrophages. The researchers also found that when macrophages were injected into diabetic rats, the insulin levels increased significantly. Additionally, the expression of glucose transporter type 2 (GLUT2), a receptor for glucose, was also increased in the diabetic rats who received macrophage injections.

Following these promising results, the researchers conducted a clinical trial involving 12 pre-diabetic patients who were injected with macrophages. The trial showed that the macrophages could be harnessed through new targeted treatments to help prevent type 2 pre-diabetic patients from suffering the physical complications and medical expenses of becoming fully diabetic.

“We are excited about the potential of this discovery to revolutionize our treatment strategies for diabetes,” Ali said. “Our findings provide a new avenue for the development of targeted therapies that could potentially improve insulin production and control blood sugar levels, which could have a significant impact on the lives of patients with diabetes.”

The NTU team’s findings suggest that macrophages could be a new and promising target for diabetes treatment, and that further research is needed to understand the mechanisms behind the macrophage-mediated insulin production and to develop safe and effective treatment strategies.

The NTU team is currently developing a clinical trial to test the potential of macrophages as a new treatment option for diabetes.

For more information, visit www.DDN-News.com
Streamlining CRISPR gene editing workflows

Individual sgRNA and library collections expand Edit-R gene editing platform

BY DDNEWS STAFF

CAMBRIDGE, U.K.—Horizon Discovery Group plc announced last year the addition of a pre-designed synthetic single guide RNA (sgRNA) option to its product range. The sgRNAs, available individually or as library collections, expand its Edit-R gene engineering platform which provides a convenient way to target DNA sequences using cationic nanoparticles.

Using synthetic sgRNAs enables researchers to achieve reliable gene knockouts in even complex, difficult-to-edit cell types and provides a high-quality, guaranteed RNA sequence. The company’s innovation, says Horizon’s head of product management, Donnelly, has enabled researchers to achieve reliable gene knockouts in even complex, difficult-to-edit cell types and provides a high-quality, guaranteed RNA sequence.

Platforms

PREDATOR technology platform

We are creating a new class of therapeutic solutions based on robotics, biotechnology and drug discovery.

The company’s platform focuses on protein engineering to generate potent biologics that can be delivered in an inactivated state so that they only activate in the target zone and don’t damage healthy tissues. Once therapeutic molecules reach the tumor microenvironment, they are selectively activated to deliver their payload, offering a new way to use cytokines and immune stimulatory antibodies at therapeutically effective doses without the risk of systemic toxicities.

With the aid of the Series A funding, Werewolf intends to focus initially on INDUKINES, its conditionally activated cytokines.

Robotics platform gets funding boost

OXFORD, U.K.—A seed funding round near the end of last year netted Arctoris Ltd. £3.2 million to advance its fully automated drug discovery platform. RT Partners led the financing, with additional participants including angel investors Patrick Pichette and Vishal Gulati, as well as industry members such as Charles Songhurst, Alexander Straub, TD Veen AS and Tanarra Capital.

“This support from industry-recognized investors and advisors will enable our team to continue to develop our revolutionary approach to drug discovery, which has been specifically designed to produce data of the highest possible quality from a broad range of biochemical, molecular biology and cell biology assays,” remarked Dr. Martin-Immanuel Bittner, co-founder and CEO of Arctoris. “Through our platform, scientists and biotechnology entrepreneurs worldwide can make discoveries faster and more efficiently, paving the way to introducing new treatments to patients sooner.”

“The length of time of the pre-diabetes phase varies from individual to individual. Some get pre-diabetes and in a matter of months will develop full-blown diabetes, while others live with pre-diabetes for years,” says Yusuf Ali of NTU’s Lee Kong Chian School of Medicine.

“Building on our discovery, we now hope to fully uncover the role lutei macrophages play, and hopefully, find ways to delay or reverse the progression of diabetes.”

NTU continued from page 3

specialized cells that identify, envelope and destroy certain cells. Pancreatic islet macrophages reside closely to beta cells, which produce insulin, responsible for the synthesis and secretion of insulin.

In pre-diabetic patients, cells in the muscles, body fat and liver start resisting the signals from insulin to remove glucose from the bloodstream and beta cells by increasing insulin secretion, Ali explains. This is further supported by an increase in the mass and number of beta cells in a process called “islet remodeling.”

Ali and his team used pre-diabetes mouse models, as well as human insulin-producing cell preparations, in the laboratory to show that the findings are translatable for humans, he says. This was conducted in accordance with Singapore’s research ethical permits and reporting guidelines.

Over the course of 16 weeks, macrophages near beta cells multiplied through cell division, according to the paper. When the scientists removed this subset of macrophages, islet remodeling and insulin levels fell, causing a transition from the pre-diabetes phase into full type 2 diabetes.

The NTU scientists believe the results of the study indicate that pancreatic islet macrophages could be successfully manipulated through new targeted treatments during the pre-diabetes phase in order to increase the supply of insulin secretion and reduce the progression of the pre-diabetes phase.

“The length of time of the pre-diabetes phase varies from individual to individual,” Ali notes. “Some get pre-diabetes and in a matter of months will develop full-blown diabetes, while others live with pre-diabetes for years. Building on our discovery, we now hope to fully uncover the role lutei macrophages play and, hopefully, find ways to delay or reverse the progression of diabetes.”

“We are honored to have received this Golden Ticket from Takeda, bringing us immediate access to a world-class bioresearch facility. It is a first step in developing Engitix’s presence in the United States, and I look forward to exploring a potential partnership in Cambridge and across the USA more widely. We are also delighted that Takeda, a leader in the area of gastrointestinal diseases, was impressed by Engitix’s ECM technology, ‘said Dr. Giuseppe Mazza, Engitix co-founder and CEO.»

EDITCONNECT: E01300

“Through our platform, scientists and biotechnology entrepreneurs worldwide can make discoveries faster and more efficiently, paving the way to introducing new treatments to patients sooner,” says Dr. Martin-Immanuel Bittner, CEO of Arctoris.

The company will use the funds to further develop its commercial operations and service portfolio. Arctoris’ service offerings provide customers with a platform for rapid success in drug discovery from target identification to candidate characterization, in addition to generating datasets for artificial intelligence model validation. The robotic laboratory features a broad range of cellular, molecular and biochemical assays, and delivers high-quality data through standardized, pre-optimized and validated processes.

A year across the pond

LONDON—Winning a Golden Ticket from Takeda Pharmaceutical Co. Ltd. may not have gotten Engitix Ltd. into World’s chocolate factory, but it did provide the company’s subsidiary, Engitix Inc., with access to LabCentral. Engitix will get to enjoy one year of lab bench space at LabCentral, a shared laboratory and office space in Cambridge, Mass., as well as first-class lab, facility and administrative support; skilled laboratory personnel; and participation in LabCentral’s training program and seminars.

Engitix intends to use the Golden Ticket to accelerate its human extracellular matrix (ECM) research in fibrosis and solid tumor disease progression.

Engitix describes its drug discovery platform as the world’s first proprietary platform based on tissue- and disease-specific human ECM scaffolds. The 3D human ECM scaffolds enable further exploration of the role of the ECM in disease pathology, thereby aiming in the identification of more relevant targets for drug and biomarker discovery, according to Engitix. The company notes that “A key current limitation in developing more effective treatments in fibrosis and for various solid cancers has been the absence of human ECM in experimental models.”

“Through our platform, scientists and biotechnology entrepreneurs worldwide can make discoveries faster and more efficiently, paving the way to introducing new treatments to patients sooner,” says Dr. Martin-Immanuel Bittner, CEO of Arctoris.
cells, which reportedly have many benefits over the models currently used by researchers and pharmaceutical companies. The models were developed by Prof. Arto Urtti’s Ocular Drug Delivery Group at the University of Eastern Finland.

The retinal pigment epithelium is located in the back of the eye, forming the outer blood-retinal barrier. Pigment epithelial cells play a key role in age-related macular degeneration, for example, which makes them an interesting target for drug therapy, the researchers say, adding that the retinal pigment epithelium also regulates the access of drugs from the blood stream into the eye and vice-versa, further highlighting the importance of this cell type for drug discovery.

Up until now, cultivated retinal pigment epithelial cell lines have lacked both pigmentation and the blood-retinal barrier, which has complicated the study of the cells. Our research group has already pigmented cell organelles, to re-pigment i.e. eat, of RPE cells. Instead of just using melanosomes to transport drugs to the cells, we were able to study how much of a drug the cells could hold on to and from the eye. In earlier cell models, the epithelial layer isn’t thick enough, allowing drugs to pass through it too quickly. This paints an erroneous picture of how drugs get transported into the patient’s eye. Earlier this year, the same research group published a study in Pharmaceuticals, presenting a new RPE cell population that had spontaneously arisen from the RPE cell line. This population forms a tight epithelial layer, resembling the real epithelial layer of the eye.

“We named this cell population after its discoverer, Senior Laboratory Technician Lea Pirkkanen, who is also one of the authors of the study. These cells are now known as LEPI cells. We decided to study them in more detail and discovered that in comparison to earlier cell models, LEPI cells are better differentiated and they form a tighter and more realistic barrier which plays a role in the aforementioned disease indications.”

LEPI

CONTINUED FROM PAGE 3

DUB

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secure exclusive rights to develop and commercialize DUB inhibitors against up to four selected targets, with Mission standing to receive success-based milestone payments and royalty payments for each successfully commercialized product. According to Dr. Anker Lundemose, CEO of Mission, the next stage of this collaboration consists of additional target validation and “a move into the discovery of small-molecule inhibitors of the DUB targets.”

“Partnering with AbbVie has been a great experience and instrumental for our research. AbbVie brings expertise and capabilities complementary to our own, and it is a testament to all involved that we have reached this important milestone,” Dr. Anker Lundemose, Mission’s CEO, said in a press release. “We have made good progress to-date and our high-quality data has enabled AbbVie to take the decision to select multiple DUBs for further investigation. We look forward to continuing to work together to discover and develop DUB inhibitors towards the treatment of Alzheimer’s and Parkinson’s diseases.”

Dr. Anker Lundemose, CEO of Mission Therapeutics

“DUBs represent a potential novel class of drug target. The collaboration with AbbVie is structured to utilize Mission’s DUB platform to identify novel DUB drug targets for AD and PD, and the subsequent development of innovative small-molecule drugs,” Lundemose tells DDNews. “To Mission’s knowledge, this is the first systematic approach to identify novel DUB drug targets for these two debilitating diseases, for which there are currently no disease-modifying treatments.”

According to current estimates, some 10 million individuals worldwide have Parkinson’s disease, and roughly 50 million individuals suffer from dementia and Alzheimer’s disease. While advancements are being made in terms of the pathology of these diseases, those numbers are on the rise, particularly in the case of Alzheimer’s disease. Alzheimer’s Disease International forecasts that the number of individuals with Alzheimer’s “will almost double every 20 years, reaching 75 million in 2030 and 135.5 million in 2050. Much of the increase will be in developing countries.” As a result, there is increased likelihood of developing either of these neurodegenerative diseases increases with age, and as people live longer and aging populations continue to grow, the market need for effective therapeutics is severe.

“The numbers of people living with Alzheimer’s and Parkinson’s is growing and there are currently no treatments capable of stopping or reversing either disease’s progression. This collaboration, using Mission’s DUB technology platform, shows promise for identifying potential drug targets and the development of new therapeutic options. We look forward to advancing our drug discovery programs with our Mission colleagues,” commented Dr. Eric Karran, vice president, Discovery Neuroscience Research, AbbVie.

Lundemose says the company is exploring the potential of DUBs in a variety of other indications in addition to neurodegenerative disease, such as kidney disease, fibrosis and rare mitochondrial diseases. One of the key targets in their pipeline is USP50, a mitochondrial-associated DUB that plays a role in the aforementioned disease indications.

As for any additional partnering efforts by the company, Lundemose notes that “This is a fast-emerging area of interest in the pharmaceutical industry broadly. Mission believes that it has the leading DUB inhibitor platform in the industry and, as a consequence, is involved in several exploratory collaboration discussions with other companies across therapeutic areas.”

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Editor’s Focus: Double helix; double bind

BY RANDALL C WILLIS

H

ave you ever accidentally stared into a bright light, only to have it leave a temporary impres-
sion in your eyes? You know, that ring of light that changes its loca-
tion every time you try to focus on it? OK, maybe that is just a harmless hobby of mine.

As I write this, we are a couple of days away from Christmas and a week from New Year’s Eve, an annual period of reflection and introspection made all the more significant because this year is another decadal transition. Adding to that significance, we are also moving into 2020, which according to cliché, should bring clarity and/or a new perspective to all past events.

For the last few weeks, I have been reflecting on the past year and on almost two decades of writing science news, and the metaphor of that elusive bright ring of light keeps cropping up in the text.

And that is a good thing, as advancements in genetic knowledge and our ability to scan, understand and change genomes will play an increasing role in human health as well as many other areas of life.

But there’s always that “but” isn’t there? But there is a risk as well when we start to get really good at something and don’t do enough of the work at the front end to curb the kind of enthusiasm that leads to potential abuse.

Nuclear physics is a wonderful field, but it also quickly led to weaponizing the atom in the form of nuclear weapons. Genetically modified organisms in agriculture has enabled harder crops in many cases but now farmers who once banked seeds away as a resource have to perpetually pay to use commodity seeds created by mega-corporations. And in the life sciences, genome sequencing leads to concerns about privacy and genetic modification data. There are changes happening in the background that prevent compa-
yny CEO Mahesh Karande and CSO Tom McCauley from fully explaining aspects of their discovery platform and prospective pipeline.

Publications and announcements were coming, they told me, but not in time for the Gene Therapy Spe-
cial Report to be published. They provided me with what information they could, but we will just have to settle for “more to come” in other aspects of their story.

On the flip side, even as I thought I had com-
pleted my research on base-editing platforms—
a variant of CRISPR, gene editing—I was pre-
sented with an evolutionary step in base editing called PRIME editing.

As 2020 approaches, we’re looking back on the year that saw heritable genome editing—and that wants to be one-upped later by someone less restrained.

Hopefully, some of us will be willing to risk being one-upped, though. We’re at a critical stage when we need to set some very clear boundaries along with very real consequences for crossing them. Genomics is one of our greatest achievements in recent history and one of our greatest hopes for better diagnostics and more cures for diseases. Let’s do it right. »

OUT OF ORDER: FOR THE BETTER

BY JEFFREY BOULEY

I

s there ANYTHING more satisfying than

finding the perfect fitting pair? Or is it genes? Or both? Aside from aimless wodd-
play, there is some metaphor in there, too. Over roughly a decade or so I

have seen mention of gene-related therapeutics, diagnostics and other research take an ever-increasing share of the word counts in this magazine and on the website.

Among the small molecules, large molecules, vacuums and such we have gene sequencing, gene editing and gene therapies standing proud and strong as well, just like jeans are found ubiquitously among the trousers, shirts, shorts and leggings in most any crowd.

In this issue alone, we have a story in Market News on page 2 that mentions the strong and growing role of gene therapies in the hemophilia market and at the other end of the mag-
azine, on page 31, news of a new technology that finally might control the spread of cancer genes—does—and in between them, starting on page 14, an entire special report focused on gene therapy. And you likely won’t go many pages in the magazine before seeing “gene” or “genetic” or “DNA” or “genomics” or any myriad relatives crop up in the text.

And that is a good thing, as advancements in genetic knowledge and our ability to scan, understand and change genomes will play an increasing role in human health as well as many other areas of life.

But there’s always that “but” isn’t there? But there is a risk as well when we start to get really good at something and don’t do enough of the work at the front end to curb the kind of enthusiasm that leads to potential abuse.

Nuclear physics is a wonderful field, but it also quickly led to weaponizing the atom in the form of nuclear weapons. Genetically modified organisms in agriculture has enabled harder crops in many cases but now farmers who once banked seeds away as a resource have to perpetually pay to use commodity seeds created by mega-corporations. And in the life sciences, genome sequencing leads to concerns about privacy and genetic modification data.

We’ve seen at least one researcher already recently use CRISPR to modify the genomes of human babies, and that’s the kind of thing that leads to messaging like this in my inbox from the Center for Genetics and Society:

“As 2020 approaches, we’re looking back on the decade that saw heritable genome editing change from science fiction to reality. Where will we be next year at this time? A decade from now? If we don’t act—and act soon—we could be looking at a future in which ‘upgraded’ genes are available only to the children of wealthy parents, and powerful muses of technology distort our beliefs about who is normal, healthy, and ‘fit’ to reproduce . . . We’re not alone in this fight: Many scientists, bioethicists, and social justice advocates agree that heritable genome editing is the most serious threat to genetic justice today.”

“I know how easy it is for us to do something before considering whether we should, or do it before someone else does because we assume it’s inevitable.”

I’m a fairly old-school journalist, so I admit that while I love my fellow humans and try to give the benefit of the doubt as much as possible, there’s a strong cynical streak in me. I know how easy it is for us to do something before considering whether we should, or do it before someone else does because we assume it’s inevi-
table.

And every time I set off to write one of these stories, I must accept that I cannot bring you much more than a snapshot of what is happen-
ing, illuminate no more than a fragment of the truth. “

I hope you enjoy this double helix; double bind.

Jeffrey Bouley

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CASE STUDY: Managing informatics challenges across distributed discovery projects

Mironid’s discovery research focuses on developing novel small-molecule drugs to exploit new insights into the PDE (phosphodiesterase) enzyme structure and function and to target degenerative kidney diseases and chronic inflammatory diseases. Autosomal dominant polycystic kidney disease (ADPKD) is an orphan genetic indication that affects approximately 250,000 patients in the European Union and United States alone and has no approved treatments, eventually leading to kidney failure for 90 percent of patients by the age of 55. Current clinical treatments do not adequately address the underlying cause of cyst formation to stop disease progression. In humans, 24 PDE4 isoforms are encoded across four distinct genes (PDE4A-D). Each of these isoforms is characterized by regions of sequence uniqueness, but follows an overarching structure of conserved regulatory domain expression which allows their grouping into “long” and “short” forms. While inhibition of PDE4 enzyme activity is a long-established method of influencing cell behavior, the inhibitors have always suffered from side effects caused by a lack of specificity of molecules binding to the catalytic site, which is near-identical among the 24 PDE4 isoforms. Small molecules that activate PDE4, on the other hand, have never been reported, until recent disclosure by Mironid [Omar et al., Proc. Natl. Acad. Sci. U.S.A. 2019; 116: 13320–13325].

Mironid has now developed insights into allosteric modulation of PDE4 enzymes that allow targeted activation or inhibition of selected subgroups of PDE4 isoforms. Of particular interest are compounds that can selectively activate PDE4 long forms, and thus decrease the levels of the second messenger, cyclic adenosine monophosphate (cAMP), in key subcellular signaling complexes; these complexes activate PDE4 long forms. The world’s first identification of selective small-molecule PDE4 long form activators provides a novel mechanism of action for the development of first-in-class molecules to treat diseases driven by aberrantly elevated levels of cAMP. These include several rare and orphan diseases, including ADPKD. The activation of PDE4 long isoforms by LoAc compounds reduces the concentration of cAMP in specific subcellular locations and reduces or reverses the formation of cysts in models of ADPKD.

“Informatics plays an important part in the drug discovery process. Proper collection, collation and reporting of results is imperative to show value from a project and provenance to the data. This can become increasingly complicated when compounds and data are being generated on multiple sites and by different organizations.”

The role of informatics

Informatics plays an important part in the drug discovery process. Proper collection, collation and reporting of results is imperative to show value from a project and provenance to the data. This can become increasingly complicated when compounds and data are being generated on multiple sites and by different organizations.

One of Mironid’s first actions was to establish an integrated, structure-searchable drug discovery database to secure its historical data and manage new data going forward. Mironid adopted the informatics platform, CDD Vault, as the company’s central data repository and informatics framework. This commercial solution is cloud-hosted for a graph-based user that can provide access to authorized users anywhere in the world from a web browser.

Over the first few months, Mironid’s history of compound development structures were transferred to the new database, in parallel with staff recruitment, setting up new labs, and scaling up the synthesis and testing of new molecules. From that point onward, new compounds, protocols and data were added to the database in real time as the standard way of sharing data within the company. This simplified the process of finding and cross-referencing compounds for both decision making and interrogating the data by chemical structure, to identify structure-activity relationships and make informed decisions for the rapid optimization of lead molecules.

In order to work in the same efficient way with CRO partners, Mironid created isolated project spaces in its CDD Vault and granted access to selected CROs’ lead scientists, allowing them to securely upload and view the data they needed. By recording compound structures and experimental results directly in CDD Vault, they eliminated the security risk of emailing files back and forth, as well as the challenges of keeping data spreadsheets synchronized and current. Mironid’s CDD Vault users have access to their CROs’ latest experimental results in real time, but only the data sets for which they individually have been authorized. This allows for a close collaboration with external partners, while ensuring that each partner has access to just the subset of data they need.

Results going forward

In 2017, Mironid secured an Innovate UK Biomedical Catalyst award. This grant has enabled the discovery of new LoAc PDE4A activators for the treatment of ADPKD. For this project, Mironid worked with a network of U.K. CROs to apply powerful computational modeling tools and expert knowledge to analyze the structure and physico-chemical properties, such as solubility and metabolic stability of the hits identified in our initial hit series. The authors of this case study are Julia M. Adam of Mironid Ltd. in North Lanarkshire, Scotland; David R. Adams of Mironid and the Institute of Chemical Sciences at Heriot-Watt University in Edinburgh, Scotland; Keith Bowers of Mironid and the Strathclyde Institute of Pharmacy and Biomedical Sciences at the University of Strathclyde in Glasgow, Scotland; David J P Henderson of Mironid and the Strathclyde Institute; and John King-Underwood of Comp Chem Resource UK of Herefordshire, England.

For some, that impermanence, that perfect imperfection, is depressing. Those people leave science (often to discover that no field is free of change). For the rest of us, however, the uncertainty and potential of tomorrow is exactly why we stay. Knowing that there is always more to know, knowing that every corner and crevice represents opportunity is what gets us up in the morning. I see it in the myriad press releases and PUBMED entries. I hear it in the passionate discussions I have with scientists and executives I interview. Serious though the conversations may be, we are all ultimately still kids in a limitless toy store.

For the love of science, however, the uncertainty and potential of tomorrow is exactly why we stay. Knowing that there is always more to know, knowing that every corner and crevice represents opportunity is what gets us up in the morning. I see it in the myriad press releases and PUBMED entries. I hear it in the passionate discussions I have with scientists and executives I interview. Serious though the conversations may be, we are all ultimately still kids in a limitless toy store.

As I left the biochemistry bench roughly as we transitioned into a new millennium, not because I couldn’t handle change, but because I wanted to explore an even wider array of change. I wanted to peer into a greater variety of dark corners than I ever could with the next chromatogram or deuterated bacterial culture.

Twenty years on, my passion for change has not wavered in the slightest (despite my periodic rumbles when my grocery store runs out of my preferred brands). And that passion will continue every time I look to social media, open PUBMED, wander a conference exhibit hall or start up a conversation.

All this to say, change is not only inevitable, it is something to be embraced. And it is something that happens whether the date is December 31, February 29 or September 12.

I, for one, love that.

Randall C Willis can be reached at willis@ddn-news.com

On a personal side note, I thank my friends Bruce Poorman and Laurence Doyle, DDNews’ publishers, for affording me these opportunities. I hope I will do this without you, but I wouldn’t want to.
**RESEARCH & DEVELOPMENT**

**BRIEFS**

**A platform partnership**

SCHEREN, Switzerland & SAN FRANCISCO—Late last year, Akers Therapeutics selected InSphero AG’s 3D InSight Human Liver Disease platform to characterize AKR-001’s physiological effects in different kinds of liver cells. This effort will evaluate AKR-001’s effects on liver metabolism, NASH-induced liver fibrosis, and pathways related to stress and cell death of hepatocytes, among other effects. AKR-001 is a novel, long-acting FGFR2 analog being developed for the treatment of NASH.

“We believe AKR-001 has unique potential among investigational NASH therapies to restore whole-body metabolic balance while also acting directly to reduce inflammation and fibrotic scarring in the liver,” commented Tim Rolph, chief scientific officer and co-founder of Akero. “With InSphero’s human in-vitro liver disease platform, we will evaluate AKR-001’s effects on human liver cells to help contextualize results from our ongoing Phase 2a clinical trial.”

**Expanding the Atlas**

CAMBRIDGE, U.K. & STOCKHOLM—Horizon Discovery Group plc and The Human Protein Atlas (HPA) have begun a partnership under which Horizon’s CRISPR-edited HAP1 knockout cell line will be integrated into the HPA Cell Atlas program. HPA plans to use 500 of Horizon’s cell models as part of large-scale protein expression and imaging studies.

Terry Pizzie, CEO of Horizon Discovery, said: “Having contributed to several thousands of publications in the field of human biology and disease, the HPA is a highly regarded knowledge provider and an expert in the field of molecular mechanisms of the human cell. We are delighted to partner with HPA to provide the robust research tools required to extend their database, and we are proud to be contributing to the expansion of this renowned open-access resource for both academia and industry.”

**OPEN TARGETS FINDS DIFFERENCES IN IMMUNE DISEASE DNA**

**BY KRISTEN SMITH**

CAMBRIDGE, U.K.—With strong financial backing from Open Targets, a battery of scientists is working to identify specific variations in DNA that correspond with different immune diseases, including asthma, multiple sclerosis and arthritis. Collating data from the Wellcome Sanger Institute, GlaxoSmithKline (GSK) and Biogen, the Open Targets initiative is locating thousands of distinctions between individuals to help science better understand why the immune system sometimes turns on itself.

Immune diseases are characterized by conditions in which the immune system mistakenly attacks the body, recognizing one’s own cells as foreign and correspondingly sending an army of proteins, or auto-antibodies, to combat the perceived invader. Scientists have long struggled to understand what causes the body to mis-identify itself, in the hopes of finding a cure for what are sometimes debilitating conditions.

Previous research has shown thousands of genetic variants that are more common in patients with immune diseases than in healthy people. According to the Sanger Institute, many of these genetic variants are

**New research on atherosclerotic plaque and T cells could offer new insight on ischemic cardiovascular events such as stroke, explain how the immune system contributes to cardiovascular events, and aid in developing new treatments to prevent them.**

**Aggravating atherosclerosis**

**Study of T cells sheds light on cardiovascular events**

**BY ILENE SCHNEIDER**

NEW YORK—Mount Sinai Health System researchers say they have demonstrated for the first time that atherosclerotic plaque, the fatty buildup in arteries that can cause heart attack and stroke, contains a high number of T cells. The research, which was published in the October 7 issue of Nature Medicine, could offer new insight on ischemic cardiovascular events, explain how the immune system contributes to cardiovascular disease and complications and aid in developing new treatments to prevent those cardiovascular events.

An important part of the immune system, T cells help to protect the body from infection and cancer, but they may also aggravate atherosclerosis. The Mount Sinai researchers performed a deep single-cell analysis of T cells in human atherosclerotic plaques and discovered that they are “all over the map.”

Researchers at the Wellcome Sanger Institute (pictured here) and elsewhere recently looked at which parts of the genome were active in three types of immune cells from healthy volunteers and compared them to the genetic variants found in different immune diseases. Researchers performed a deep single-cell analysis of T cells in human atherosclerotic plaques and discovered that they are “all over the map.”

**Akoya finds $50M more in financing**

**Funding will support continued commercialization of Akoya’s spatial biology platforms**

**BY MEL J. YEATES**

MENLO PARK, Calif.—Akoya Biosciences Inc. announced in early December the completion of a $50 million financing round from both new and existing investors. The round will fund the expansion of commercial and operational resources, as well as continued product development of Akoya’s CODEX and Phenoptics platforms for spatial biology.

“Akoya is proud of and thankful for our new partners, as well as our long-term relationship with Telegraph Hill Partners,” says Brian McKellog, CEO of Akoya. “These new partnerships validate Akoya’s product lines and commercial trajectory.”

The financing was led by Piper Jaffray Merchant Banking, a division of Piper Jaffray, with continued participation from Telegraph Hill Partners. New strategic partners include Agilent Technologies Inc. and Innovatus Capital Partners LLC. This financing round follows Akoya’s September 2018 Series C funding, which was used to support the acquisition of the Phenoptics portfolio from PerkinElmer Inc.

“We are excited to support Akoya’s efforts to commercialize multiplexed imaging solutions to unlock the full potential of spatial biology,” noted Claus Ekmann, managing director at Innovatus.

The new financing will enable further product development of the CODEX and Phenoptics platforms for multiplexed immunofluorescence imaging and analysis, commercial expansion and the scale-up of operations and manufacturing. These expansions are driven by dramatic growth in the immuno-oncology market. There is mounting evidence that spatial analysis using multiplex
immune cells in plaque, which reportedly had never been done before in humans.

According to the paper in Nature Medicine, “Atherosclerosis is driven by multifaceted contributions of the immune system within the circulation and at vascular focal sites. However, specific characteristics of dysregulated immune cells within atherosclerotic lesions that lead to clinical events such as ischemic stroke or myocardial infarction are poorly understood. Here, using single-cell proteomic and transcriptomic analyses, we uncovered distinct features of both T cells and macrophages in carotid artery plaques of patients with clinically symptomatic disease (recent stroke or transient ischemic attack) compared to asymptomatic disease (no recent stroke).”

“This is a first study towards the ultimate goal of building a single-cell immune atlas of human atherosclerosis. By profiling individual cells in blood and atherosclerotic plaques, we found new inflammatory alterations in plaques related to cardiovascular events,” explained lead investigator Dr. Chiara Giannarelli, an assistant professor of medicine (cardiology) and genetics and genomic sciences at the Icahn School of Medicine at Mount Sinai. “We found that T cells, a cell type known to fight infections and cancer, may have an unanticipated important role in driving atherosclerotic cardiovascular disease. Exploring the diversity of T cells in human atherosclerosis may lead to new therapeutics in the future.”

Mount Sinai researchers studied patients undergoing carotid artery surgery and found an abundance of T cells and an increased infiltration of a subset of pro-inflammatory T cells called CD4+ in patients who had suffered a recent stroke.

The researchers said that plaques from symptomatic patients were “characterized by a distinct subset of CD4+ T cells and by T cells that were activated and differentiated.” Some T cell subsets in these plaques showed markers of T cell exhaustion. Macrophages from these plaques had alternatively activated phenotypes, “including subsets associated with plaque vulnerability.” In plaques from patients who were asymptomatic, T cells and macrophages that were activated displayed evidence of interleukin-1β signaling.

Other subsets of T cells, including CD8+ T cells, were infiltrating plaques by being highly active or inflammatory, differentiated and highly specialized to the plaque environment, or exhausted and not killing disease cells. The exhausted T cells expressed PD-1, a protein that usually prevents T cells from killing other cells. CD8+ T-cells usually recognize and kill cancer cells or cells infected by viruses. All of these cell subsets could increase plaque inflammation in stroke patients, possibly putting these patients at a higher risk of future cardiac events.

“These findings suggest that PD-1 inhibitors, a breakthrough treatment that is used in cancer to turn T-cells against the tumor, may also activate exhausted T-cells in plaque,” noted Giannarelli. “This could increase plaque inflammation and possibly the risk for cardiovascular events in patients.”

Co-author Dr. Miriam Merad, director of the Precision Immunology Institute and director of the Human Immune Monitoring Center at the Icahn School of Medicine, described the study as “a perfect example of how single-cell mapping of human disease lesions can transform our understanding of disease pathophysiology,” adding that it “generated a new hypothesis about disease drivers that we hope will lead to novel therapies.”

Dr. Michelle Olive, program officer at the National Heart, Lung, and Blood Institute Division of Cardiovascular Sciences, concluded that the research “shows the molecular connections linking blood and cellular make-up of the atherosclerotic plaque within the same individual and the clinical outcome” and demonstrates “that cutting-edge techniques like CyTOF and other single-cell technologies are useful in charting the landscape of atherosclerotic plaques.”

**CONTINUED FROM PAGE 8**

**RESEARCH & DEVELOPMENT**

**SET VOLUMES IN THE BLINK OF AN EYE**

**INSTEAD OF A TWIST OF THE WRIST**

**EVOLVE Manual Pipette**

Unlike traditional pipettes which utilize a single rotating plunger to set volumes, the EVOLVE features three dials for setting each individual volume digit. This revolutionary approach allows users to set volumes more than ten times faster.
Oral therapy for hemophilia

Bayer enters into collaboration with Children's Hospital of Philadelphia on novel small-molecule drugs

BY DON NEWS STAFF
WHIPPANY, N.J.—Bayer announced in Hospital of Philadelphia on collaboration with Children's Bayer enters into Oral therapy for hemophilia more than 400,000 people live with hemophilia A and B. The partnership will combine CHOP's expertise in hemophilia and coagulation and Bayer's research capabilities. Hemophilia is a genetic bleeding disorder in which one of the clotting proteins needed to form blood clots in the body is missing or defective. Worldwide, it is estimated that more than 400,000 people live with hemophilia and approximately 75 percent of them receive inadequate treatment. The main treatment for hemophilia is called replacement therapy and is often administered multiple times a week to help replace the clotting factor that's missing or low. An orally available small molecule for the treatment of hemophilia would be a completely new modality in the market, and has the potential to remove the burden of frequent injections from patients. "Bayer is committed to investing and researching the next-generation of groundbreaking therapies. Small-molecule therapies could help thousands of people with hemophilia A and B, and we are looking forward to combining our strength in hemophilia research with Children's Hospital of Philadelphia, which is a leading institution in basic and clinical research in the field of hemophilia," said Dr. Jorg Moeller, member of the executive committee of Bayer's Pharmaceuticaals Division and head of research and development. "This innovative approach is unprecedented in pharmaceutical history and would leverage significant opportunities for continued innovation in hemophilia." Under the terms of the agreement, Bayer is investing $5 million in the joint research over three years, with the option of continuing the collaboration with the agreement of both parties. Bayer will have an option to exclusively license the collaboration results. Bayer has a strong background in hemophilia products, with Jivi at the forefront of the hemophilia replacement therapies market. The new research alliance with CHOP, a world-renowned pediatric research center, has the potential to change the treatment paradigm for patients, the partners say. In addition, Bayer is currently developing a gene therapy treatment for hemophilia A patients, which could radically reduce the frequency of treatment these patients have to undergo.

There is mounting evidence that spatial analysis using multiplex immunofluorescence—such as with Akoya Biosciences' CODEX and Phenoptics platforms—is critical to understanding cancer's complexity and could potentially provide more power for predicting patient response to immunotherapies. "The Phenoptics platform, including the Vectra Polaris system, provides the industry standard for end-to-end, whole tissue sample, " he continues. "With the rapid advancement in immunotherapy, today's researchers require next-generation tools to discover novel biomarkers and high-throughput, reproducible platforms that can scale to the large datasets required in clinical research. The CODEX platform as a discovery tool enables simultaneous analysis of over 40 individual markers, while maintaining the tissue quality, allowing researchers to gain a more comprehensive understanding of a tissue sample," he continues. "The Phenoptics platform, including the Vectra Polaris system, provides the industry standard for end-to-end, whole slide analysis of up to seven colors and more than 30 slides per day. Discoveries made with the CODEX system can be rapidly turned into high-throughput assays for clinical and translational studies."

When asked what is next for the two platforms, McKelligon states, "Akoya is making great strides in the advancement of both platforms. Key for the CODEX platform is a broad expansion to the antibody content to enable new application areas such as neurobiology and other challenging tissue types. At STIC, we showcased novel amplification methods to increase the sensitivity of the CODEX assay, which will be important for detection of lower expressed biomarkers. On the Phenoptics platform, our focus is to remove the burden of frequent injections from patients. Bayer is committed to investing and researching the next-generation of groundbreaking therapies. Small-molecule therapies could help thousands of people with hemophilia A and B, and we are looking forward to combining our strength in hemophilia research with Children's Hospital of Philadelphia, which is a leading institution in basic and clinical research in the field of hemophilia," said Dr. Jorg Moeller, member of the executive committee of Bayer's Pharmaceuticaals Division and head of research and development. "This innovative approach is unprecedented in pharmaceutical history and would leverage significant opportunities for continued innovation in hemophilia."

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BRIEFS

TOXICITY PREDICTIONS

BOSTON—When evaluated with eight previously studied drugs, Emulate Inc.’s Liver-Chip was able to accurately model and predict human toxicity, the company announced in November. In addition to predicting liver toxicity differences between humans, dogs and rats, the Liver-Chip was also able to model the mechanism of action for hepatotoxicity and measure relevant clinical biomarkers. This research examined drugs that had advanced to human trials with no signs of toxicity in animal studies, but that were then halted during in-human studies due to safety concerns. The Liver-Chip accurately predicted the drugs that demonstrated human toxicity despite not showing any hepatotoxicity concerns in animal studies. The results, published in Science Translational Medicine, were co-authored by researchers from AstraZeneca, Janssen Research & Development, LLC, the Wyss Institute for Biologically Inspired Engineering at Harvard University, and Emulate.

OB-002 shrinks tumors, bone metastases

OTTAWA, Ontario—Orion Biotechnology Canada Ltd. has reported that in a mouse model of breast cancer, OB-002 significantly reduced bone metastasis. Mice that received 20mg/kg saw significantly reduced primary tumor volume, and those that received 80mg/kg also saw a noticeable reduction in spinal bone metastasis. Dr. Ian McGowan, Orion’s chief medical officer, commented in part that “Unfortunately, bone is the most common site of metastatic breast cancer (Onising AG et al., Clin Exp Metastasis 2017), and approximately 70 percent of women dying from breast cancer have bone metastases (Awoilaran O et al., Breast 2010). Clearly, any product that has the potential to reduce breast cancer-associated bone metastasis would be a major advance in the field.”

TARGETING TOUGH TUMORS

Femtogenix payload platform has favorable toxicity profile

BY ILENE SCHNEIDER

HARPENDORF, U.K.—Femtogenix Ltd., a biotechnology company developing DNA-interactive antibody-drug conjugate (ADC) payloads, has presented data on ADCs with reduced potency payloads that have the potential to be safe and effective on difficult-to-treat solid tumors. Data from a reduced potency, sequence-selective DNA mono-alkylate analogue from the company’s pyridinobenzodiazepine (PDD) ADC payload platform in solid tumor models demonstrate potent efficacy and a favorable toxicity profile. According to Femtogenix, this represents a promising new approach in ADC development, specifically for the treatment of solid tumor malignancies. The data were presented at AACR-NCI-EORTC International Conference on Molecular Targets & Cancer Therapeutics in Boston in October.

When attached to antibodies or other targeted moieties, the PDD payload platform enables reversible/irreversible DNA minor groove binding, in a sequence-active manner. This property results in highly targeted cytotoxicity toward tumor cells, the company said. Payloads are designed to have a novel mechanism of action and intellectual property space as compared to existing ADCs.

A model replacement?

Heart-on-a-Chip technology predicts preclinical systolic, diastolic in-vivo observations for cardiac drug candidate

BY MEL J. YEATES

NEW YORK—TARA Biosystems, Inc. has reported in-vivo and in-vitro functional data from a study of an investigational candidate, MYK-491, showing that TARA’s human iPSC-derived TARA CONTINUED ON PAGE 12

Knowing the score

New application helps authors, publishers address heightened reproducibility and transparency standards

BY JIM CIRIGLIANO

SAN DIEGO—SciCrunch Inc., a scientific researcher content management system and collaboratively edited knowledge base of scientific resources hosted by the University of California, San Diego (UCSD), has announced the release of SciScore, an application designed to generate a score and supporting report that an agency, publisher or author may use to identify whether key areas of reproducibility and transparency are addressed in a manuscript. SciScore is reportedly the first and only working transparency standards application that has favorable novelty, “says Dr. Anita Bandrowski, neuroscience researcher at UCSD and the founder and CEO of SciCrunch. “This is a new application of its kind, designed to be used in support of the preclinical scientific research community’s pursuit of reproducibility and transparency.

In January 2016, the U.S. National Institutes of Health (NIH) introduced new grant review guidelines that placed greater emphasis on areas of reproducibility and transparency, and in the process, changed the way in which grants are awarded. In response, many scientific journals—notably PLoS, IBC, elife, AACR, MBio and GSA—have revised their author guidelines to encourage researchers to include and emphasize the elements required for reproducibility and transparency.

“The National Institutes of Health has changed grant guidelines in 2016 to refocus the granting mechanism on rigor from novelty,” says Dr. Anita Bandrowski, neuroscience researcher at UCSD and the founder and CEO of SciCrunch. “This is a SCORE CONTINUED ON PAGE 13
Immunic presents data on IMU-856 at Crohn's and colitis conference

IMU-856 might address a root cause of inflammatory bowel disease without impairing immune system

**BY DDNEWS STAFF**

NEW YORK—December saw Immunic Inc., a clinical-stage biopharmaceutical company focused on developing oral therapies for the treatment of chronic inflammatory and autoimmune diseases, announce that Dr. Hella Kohlhof, chief scientific officer of Immunic, presented data at the Crohn’s and Colitis conference hosted by the Crohn’s and Colitis Foundation.

The presentation, entitled, “IMU-856: A Small Molecule Modulator Restoring the Gut Barrier Function,” was given as part of the “Small & Large Molecule” session that showcased innovative product development programs in inflammatory bowel disease (IBD). Kohlhof’s presentation highlighted the potential of IMU-856 to revolutionize the treatment of multiple diseases related to intestinal barrier function.

IMU-856, which Immunic believes to be novel and highly innovative, is an orally available, small-molecule modulator that targets a yet undiscovered protein which serves as a transcriptional regulator of the intestinal barrier function. Based on preclinical data, the compound appears to represent a new and potentially disruptive approach for the treatment of intestinal diseases by potentially restoring the intestinal barrier function while maintaining immunocompetency.

Highlights of the presentation included:
- IMU-856 is an epigenetic regulator that appears to influence the tightly regulated network of genes and proteins associated with intestinal epithelial cell interaction and adhesion
- IMU-856 has shown target modulation at very low concentrations in both cellular and non-cellular models

**TARA**

**CONTINUED FROM PAGE 11**

organ-on-a-chip technology can directly measure in-vivo cardiac performance. These data were presented at the American Heart Association’s Scientific Sessions in Philadelphia, in November.

“The Biowire II platform generates three-dimensional tissues from induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and subjects them to a biomimetic maturation process. The resulting tissues exhibit physiological properties similar to that of human cardiac muscle and respond to a wide range of drugs used to treat cardiac diseases. Unlike other organ-on-a-chip platforms, the Biowire II platform directly measures the force with which these engineered tissues contract,” said Miitsh Ushio, CEO of TARA Biosystems. “Unlike other organ-on-a-chip platforms, the Biowire II platform directly measures the force with which these engineered tissues contract.”

“TARA’s human heart-on-a-chip technology provided confirmatory preclinical evidence of what was found in our other preclinical and clinical studies: MYK-491 appears to increase systolic contractility without impacting diastolic relaxation,” Ushio continues. “Replicating assays typically conducted on human heart muscle can really make an impact on the translation of clinical compounds, ” said Dr. Michael P. Graziano, chief scientific officer of TARA Biosystems. “Replicating complex physiology in systems that up to now could only be seen in animals positions our technology as a faster, cheaper and more human-relevant alternative to animal testing.”

In the study, the effects of MYK-491 were evaluated in instrumented canine models and TARA’s human cardiac organoid model. The results indicate agreement between the two models—both showed improvements in systolic elastance (force production), with negligible effects on diastolic function.

Both systolic and diastolic tension are dysregulated in patients with heart disease and, given their load dependency, systolic and diastolic mechanics have been difficult to measure in an in vitro setting. It typically requires studies in large animals with advanced instrumentation to capture such complex, integrated functional effects. TARA’s organ-on-a-chip platform could offer an in-vitro alternative to collect such measurements in a human setting.
TOUGH CONTINUED FROM PAGE 11
DNA-interactive payloads, to have minimal hydrophobicity and to be resistant to P-Glycoprotein pumps in tumor cells. These data show that the payload potency profile has a favorable toxicity profile in rats, potent in-vivo efficacy (MED < 1 mg/kg) and improved tolerability (i.e., MTD of 40 mg/kg) in solid tumor models when conjugated to antibody-drug conjugate platform. In-vivo toxicity profile and high therapeutic window are combined with the ability to increase drug-to-target ratio beyond the traditional limit for increased conjugation to antibodies.

According to Prof. David Thurston, chief scientific officer of Femtogenix, “The favorable hydrophobicity profile of the low potency mono-alkylator and its ease of conjugation, along with the significant in-vivo efficacy and tolerability of the ADCs produced, suggest that this payload represents a promising new approach in ADC development, specifically for the treatment of solid tumor malignancies.”

Femtogenix has generated extensive data on mechanism of action of the ADC payload, illustrating a primary mechanism of action DNA alkylation, combined with an ability to inhibit transcription factors. The molecules have been designed through proprietary molecular modeling methodologies to maximize interaction within the DNA minor groove. Researchers believe that payloads with different potencies and modes of action might be used for specific target situations.

The announcement followed data presented earlier at World ADC 2019, San Diego, verifying the favorable toxicity profile and potent efficacy of Femtogenix’s PDD ADC payload platform in tumor model cells. The studies demonstrated the efficacy and cytotoxicity of the sequence-selective DNA-interactive payloads toward tumor cells. At World ADC, Femtogenix described details of its latest payload molecules for ADC use and demonstrate that high potency mono-alkylators derived through the PDD platform have a favorable toxicity profile in rats, combined with potent in-vivo efficacy (MED < 1 mg/kg) and excellent tolerability (MTD > 10 mg/kg) when conjugated to antibodies. Femtogenix also introduced a new class of DNA cross-linking ADC payloads at the World ADC conference, based on its proprietary PDD platform with potent in-vivo efficacy and substantially enhanced tolerability profiles compared to competing technologies.

According to Dr. Christopher Kightley, CEO of Femtogenix, “These data show that our PDD technology overcomes many of the limitations of existing approaches to ADC payloads. The toxicity profile and ease of conjugation of the PDD mono-alkylators, along with their novel mechanism of action and significant in-vivo and in-vitro efficacy, suggest they represent a promising new payload class. We are delighted with the progress as we conclude significant collaborations with pharma partners who will help us achieve the practical application of our innovative approach to a new generation of ADCs.”

Using a variety of techniques, including DNA footprinting and FRET studies, Femtogenix has generated extensive data on the specific interaction of these payload molecules with DNA. The molecules have been designed through molecular modeling methodologies to maximize interaction within the DNA minor groove. The design methodology, which has led to the creation of ADC payloads with a range of potencies, has also been used to generate novel DNA cross-linking payloads that form unique DNA adduct structures with differing modes of action. Payloads with differing potencies and modes of action may be applicable to particular uses or specific target situations.

SCORE CONTINUED FROM PAGE 11

The tool is a working application of its kind, designed to be used in support of the preclinical scientific research community’s pursuit of reproducibility and transparency.

According to SciCrunch, major publishers—including Wiley & Sons, NatureResearch and eLife—are currently piloting the SciScore application.

Manuscripts submitted for analysis are removed from the company’s cloud server almost immediately after scoring is completed, keeping the authors’ yet-unpublished information secure and private.

“We will continue to improve the tool as we are able,” says Bandrowski. “We have been talking to the Materials Design Analysis Reporting group, who are creating a checklist that should be applicable to many journals to see which aspects of the checklist we might go after next. Ideally, a checklist like this would be implemented across many publishers consistently, and SciScore would be able to verify the author’s response, improving the scientific literature and making it more consistent among publishers.”

“I believe that more rigorous science will benefit all of society,” she adds. “I don’t think that it is genuine to say ‘we will cure cancer with the next 10 years’ studies that are more rigorous should enable clinical trials to be based on more sound science.”

“SciScore is the first and only working application of its kind, designed to be used in support of the preclinical scientific research community’s pursuit of reproducibility and transparency.”

CONTINUED FROM PAGE 11

PRECLINICAL

SM08502 CONTINUED FROM PAGE 11

gastrointestinal tumors, including pancreatic cancer (for which SM08502 received orphan drug designation from the FDA in January 2019), prostate cancer, breast cancer, gastric cancer and hepato-cellular carcinoma,” he continues.

Regulation of CLK2 and CLK3 is a new strategy that leads to modulation of Wnt pathway signaling in cancer. The paper focuses on SM08502, currently being evaluated in a Phase 1 study in the United States. The study is designed to assess the safety and pharmacokinetics of SM08502 in patients with multiple types of advanced solid tumors.

According to Yazici, “It is well documented that aberrant Wnt pathway signaling occurs in many types of cancer, including around 90 percent of colorectal cancers, but the complexity of the Wnt signaling pathway has presented challenges for developing and efficacious Wnt signaling modulators for cancer treatment to date.”

“These published data identified a novel mechanism for impacting Wnt pathway signaling via potent inhibition of CLK2 and CLK3 and subsequent effects on alternative splicing. Our first-in-class CLK inhibitor, SM08502, had strong antitumor effects and diminished aberrant Wnt pathway activity in these mouse models and demonstrated its potential to treat gastrointestinal cancers,” he added.

“We look forward to the availability of data from our ongoing Phase 1 safety and pharmacokinetics trial in subjects with advanced solid tumors.”

Data highlights of the study include the information that CLK3 is a potential oncogenic kinase, given the profound inhibition of tumor growth (i.e., CLK3 KO sw480 clones),” the authors write. “Knockdown of CLK3 in these clones demonstrated inhibition of SRSF6 phosphorylation despite the presence of CLK3 or CLK2, which further supports the importance of CLK3 inhibition for the overall anti-tumor mechanism of SM08502.”

“Not only did this study highlight the potential of SM08502 for the treatment of gastrointestinal tumors, but it also highlights the expertise of Samumed’s scientists in the study of Wnt signaling mechanisms,” Yazici notes. “As such, an important discovery from the development of SM08502 is the identification of a previously unknown method for reducing Wnt signaling in tumors, through CLK. If the preclinical results...showing antitumor effects in mice translate into humans, SM08502 could represent an important breakthrough not only for the treatment of gastrointestinal tumors, but also for the overall development of Wnt-targeting drugs.”

“This Phase 1 study...is currently ongoing. Top-line results are expected in 2020. After the Phase 1 dose escalation study, we plan to expand the study for SM08502, including but not limited to gastrointestinal malignancies, starting in 2020.” he concludes.
**SPECIAL REPORT**

**FROM GENE TO BASE**

For genetic disorders, the progression from small-molecule and biologics interventions to cell and gene therapies has been an effort to find deeper and longer-lasting treatments that—in their ultimate form—could be curative.

Some disorders have been more amenable to genetic exploration (e.g., stable monogenic disorders), whereas others have been more intractable (e.g., molecularly heterogeneous tumors).

The University of Victoria’s Francis Choy and Chloe Christensen work in the former category, focusing on mucopolysaccharidoses (MPSs), lysosomal storage disorders where the absence of a single metabolic enzyme leads to a buildup of toxic byproducts. Effectively, the cellular garbage disposal is broken, and the molecular trash overwhelms the cell.

“Enzyme replacement therapy [ERT] has really been the interest over the years for lysosomal diseases and MPS in particular,” Christensen explains, but this approach offers a variety of limitations, not the least of which is the inability of ERT to cross the blood-brain barrier (BBB).

Thus, for conditions like MPS IIIB (aka Sanfilippo syndrome), ERT can ameliorate the bodily impacts of the disorder, but not the neurological impacts.

“There is also the issue of ERT being a chronic therapy, something that needs to be used over time,” she continues. “Patients have to go back for repeat treatments, and for that reason, as well as because the MPSs are quite rare, ERT can be very expensive.”

To find a longer-lasting solution, Choy’s lab and others have looked at gene therapy as a potential solution, using vehicles like adeno-associated viruses (AAVs) to deliver the missing genes to cells where they would produce the deficient enzyme.

“Even more recently, more interest has been in gene replacement therapies, where the gene can actually be knocked-in to the genome of the patient,” Christensen notes, pointing to the recent CHAMPI-ONS and EMPOWERS clinical...
“Once edited for a patient-specific mutation, you can take those cells, differentiate them into neuronal and glial precursors, and deliver them back into the patient using intracerebral transplantation. Then, hopefully, those precursors would turn into neurons and glia, be able to produce functional enzyme, and secrete the enzyme to be taken up by existing neurons in the patient brain.”

Chloe Christensen of the University of Victoria
GENE-cont’d from page 15

The 5’-UTR region of BRCA1 might regulate the transcription level, and several mutations in the 5’-UTR region are known as pathogenic variants,” the researchers stated. “To further validate the c.−97 C > T variant, we performed a luciferase reporter assay in HEK293T/17 cells, which showed that the c.−97 C > T mutation in the 5’-UTR caused a two-fold down-regulation of gene expression.”

The identification of a novel potentially pathogenic mutation in the 5’-UTR region of BRCA1, they pressed, highlighted the importance of the UTR region for clinical genetic testing.

Base editors continue to undergo development, whether to increase efficiency, enhance specificity or to potentially broaden activity.

As the Zhang studies suggest, base editors are not free of challenges either, and whereas those experiments could accommodate multiple and varied A > G transitions within a single codon, potential use of base editing in gene therapy might not.

“I would say that the biggest challenge is currently around what we call bystander edits,” explains Freeman, which occur when there are multiple target residues within the editing window, as above.

“This is of particular concern when the aim is to precisely repair a point mutation, for example, as a gene therapy for a monogenic disorder, which would be repaired by transition mutation,” he says, “but is less of a concern when the application is to knockout a gene, or cause exon skipping.”

Another challenge, he suggests, is delivery, which is a concern echoed by Christensen.

“For the CRISPR/Cas9 system, the best method so far seems to be the delivery of the actual Cas9 nuclease in conjunction with an already-present guide RNA, instead of using a plasmid,” Christensen says. “Unfortunately, for base editors, because they’re so new they are only available from Addgene as plasmids, and it’s a very large plasmid.”

“So, even though transfection methods have really come a long way in recent decades, it is still very challenging to get a 10-kb plasmid into hard-to-transfect cells,” she continues. “And then beyond that, to ensure that this plasmid is actually transcribed and translated into the appropriate base-editor protein.”

Christensen sees one of the big next steps for the field coming with the production and commercialization of the base-editor protein.

“Delivery is also why the predicts most of the patient therapy focus turning toward ex vivo cell modification—as the Choy lab is pursuing—rather than direct delivery to patients. This would allow researchers to prescreen cell therapies for any off-target modifications.”

In a recent review, Choy, Christensen and colleague Rhea Ashmead noted the challenge with off-target modification and described efforts in another lab to modify BE3 to reduce off-target effects without reducing base-editing efficiency, variants given the applicable Selective Curbing of Unwanted RNA Editing, or SECURE.

Existing base editors also suffer from limitations in the types of mutations they can correct.

According to Choy, “The base editor relies on the deaminase enzyme to change the mutated base to the correct one, but right now it is limited to changes of a purine to pyrimidine or pyrimidine to purine. But if the original sequence is a purine that mutated to a pyrimidine, then the deaminase will not be able to correct it.”

But even that challenge is being addressed with the introduction of Prime editing a couple months ago.

Here, in place of a deaminase, Cas9 has been modified with a reverse transcriptase, and the guide RNA has been extended to include a segment with homology to the corrected gene sequence, facilitating the repair via reverse transcription.

“Prime editors are like a hybrid of the base editor and the CRISPR/Cas9 HDR,” says Christensen. “It can use this correction template to fix any type of mutation you have at that site.”

That said, Freeman adds, there are concerns over the editing efficiency and rate of DSB formation relative to base editing, so base editing may be a more appropriate technology to use in engineering cells destined for therapeutic use.

“I see Prime editing as being an exceptionally complementary technology to base editing,” he presses. “Where suitable—that is, appropriate transition mutations and multi-gene knockouts—I believe base editing to be the preferred technology. Where base editing is not applicable—that is, transversion mutations, small insertions/deletions—then Prime becomes the best available technology.”

Where genome and base editing may provide significant inroads in dealing with monogenic disorders, however, life becomes more complicated when one begins to explore multifactorial conditions, whether involving multiple mutations or metabolic pathways.

To address these situations, some researchers have turned to engineering.

FROM GENE TO CIRCUIT

“The way we have traditionally thought about biology is very static,” offers Senti Bio CEO Tim Lu. “Here’s a gene, the gene has a function. You knock out the gene or you over-express the gene.

“Biological systems are a lot more dynamic than that. It should be obvious, but it is something that the field has really come to grips with.”

As much as biology is about what genes are expressed, it is even more about how they are expressed, when they are expressed and in what combinations of expression with other genes. That dynamic interplay, he continues, is at the core of everything, from physiological development to disease pathology.

This is not to say Lu dismisses the recent advances in cell and gene therapy. He sees those as truly
processes in order to produce sophisticated decision-making engineering principles to modify living science than cell biology. More of reminiscent of computer language, Barbara Jusiak—reviewed the leagues from MIT—Ming-Ru Wu and colleagues. The goal for what we’re trying to do is provide the technologies to build those dynamic therapies, “So, can we build gene circuits reliant on logic gates that define their response to their environment?”

And like computer circuits, these gene circuits rely on logic gates and the inputs to the systems. “The inputs to a circuit can be exogenous, such as user-provided small molecules or specific wavelengths of light, Cytidine deaminase, or endogenous, such as transcripts or proteins that can distinguish between cell types of interest.” Human cells are not computer chips, however, so designing highly functional gene circuits continues to be challenging.

“Often, when we try to gauge any project, it is really about number one, having the tools available, ones that you’ve built before and know work reasonably well,” Lu explains. “Number two is being able to rapidly design, build and test,” he continues. “We take a very engineering approach here, where we’re not typically just looking at a single construct. We’re trying to develop methods where we can look at hundreds, thousands or tens of thousands of different variants, and then rapidly determine which ones work well, which ones don’t.”

The researchers were able to develop tools that can correctly and reliably bring the company success. The more times you can go around that cycle, the faster you can converge on the final system. An example of this is Lu’s efforts with The Hebrew University of Jerusalem’s Yuval Tabach and others to identify synthetic promoters with enhanced cell-state specificity (SPECS), which they described in 2019. The authors reported that earlier efforts to design SPECS consisted of tandem repeats of transcription factor binding sites (TF-Bs) for a handful of TFs known to be active only in the cell state of interest. Thus, the SPECS were largely built from prior knowledge.

“I would say that the biggest challenge is currently around what are called bystander edits. This is of particular concern when the aim is to precisely repair a point mutation—for example, as a gene therapy for a monogenic disorder, which would be repaired by transition mutation, but is less of a concern when the application is to knockout a gene, or cause exon skipping.”

Jamie Freeman of Horizon Discovery says the company takes a

**GENOMIC SPELLCHECK** An evolution of CRISPR/Cas9 gene editing, base-editing uses a deaminase moiety to create single base transitions from C to T or A to G, avoiding potentially damaging DNA double-strand breaks.

transformation for certain diseases, like monogenic disorders or certain cancers where a simple, single-target approach is sufficient.

“But if we want to go toward more complex diseases, solid tumors, for example, that likely involve multiple targets we have to hit, or diseases that may involve more than one target or may have a narrow therapeutic window,” Lu clarifies. “Those are all things that are going to require therapies that are more sophisticated and more programmable. So that’s really what the field of synthetic biology is about.”

And that is why he moved from MIT to co-found Senti Bio. “The goal for what we’re trying to do is provide the technologies to build those dynamic therapies,” he explains. “So, can we build gene therapies that can be turned on and off? Can we build gene therapies that are highly specific to a certain cell type? Can we build gene therapies that are conditionally on during a period of time?”

Senti Bio is tackling this issue with gene circuits.

Earlier this year, Lu and two colleagues from MIT—Ming-Ru Wu and Barbara Jusiak—reviewed the use of gene circuits vs. cancer, and they quickly jumped into language more of reminiscent of computer science than cell biology. “Synthetic biology applies engineering principles to modify living cells, enabling them to perform sophisticated decision-making processes in order to produce a user-defined outcome,” the authors wrote. “This approach often involves programming artificial multi-gene circuits that consist of three components: a sensor that detects user-defined input(s), a processor that decides on the response to the inputs, and an actuator that produces the desired response.”

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It is that design/build/test/learn cycle that he feels will ultimately bring the company success. The more times you can go around that cycle, the faster you can converge on the final system. An example of this is Lu’s efforts with The Hebrew University of Jerusalem’s Yuval Tabach and others to identify synthetic promoters with enhanced cell-state specificity (SPECS), which they described in 2019. The authors reported that earlier efforts to design SPECS consisted of tandem repeats of transcription factor binding sites (TF-Bs) for a handful of TFs known to be active only in the cell state of interest. Thus, the SPECS were largely built from prior knowledge.

Instead, the researchers wanted to design a high-throughput experimental and computational screen that did not require prior information.

“For this purpose, we designed a library of synthetic promoters that corresponds to 6,107 eukaryotic TF-Bs reported in two databases,” they explained. “Each construct in the library comprises tandem repeats of a single TF-B encoded upstream of an adenovirus minimal promoter to control the expression of mKate2, a fluorescent protein.” The team then used FACS, next-generation sequencing and machine-learning to identify optimal SPECS.

The researchers were able to identify promoters with up to 1,000-fold activity differential between the cell states of interest and their counterparts, highlighting “(i) distinct spatiotemporal activity in an organoid differentiation model; (ii) specificity for either a breast cancer or a normal breast cell line; and (iii) discrimination of stem-like glioblastoma cells from their differentiated counterparts.” The high-throughput identification of SPECS also addresses another key factor in gene circuit design: modularity.

“Think modularity is one of the central things you need in engineering those complex systems,” Lu says. “It’s true for computers. In biology, it would be great if things were perfectly modular, but in reality, it is never that clean.” Again, he presses, design is key.

“How do you design feedback loops or certain architectures to maximize modularity?” he asks. “And then on top of that, having that downstream optimization effort to make sure that indeed these components when you put them together do work for the application of interest is important.”

Lu says the company takes a

**GENE CONTINUED ON PAGE 18**
SPECIAL REPORT

CREDIT: FRANCIS CHOY

Sanfilippo syndrome (MPS IIIB).

“...we can really rapidly translate toward the clinic.”

He acknowledges, however, that even these vectors have their limits. “So, the additional design constraint for some of these early gene circuits we’re building is not only to optimize for function, but also to minimize size,” he remarks. “That’s actually one of the reasons we came up with the synthetic promoter platform, because the size of the actual promoters makes a difference in how much you can package in [the vector].”

Senti Bio is hardly alone in designing gene circuits that need to tackle this issue. In 2019, Tsinghua University’s Zhen Xie and colleagues, including researchers at Syngentech, described their efforts to develop oncolytic adenoviral approaches to cancer immunotherapy. Focusing not just on expression of immune effector molecules like GM-CSF, IL-2 and anti-PD-1 or anti-PD-L1 checkpoint inhibitors, the researchers also looked to control adenoviral replication in hepatocellular carcinoma (HCC), both in culture and in mice.

The researchers observed that non-replicating adenovirus constructs failed to inhibit tumor growth, whereas replication-competent constructs strongly inhibited tumor growth. For example, more than 80 percent of mice receiving the base by two CTCF proteins, zinc-finger proteins that come together to form this insulated loop,” explains Omega CEO Mahesh Karande.

In mapping the more than 15,000 IGDs in human cells, Omega researchers have come to realize that much of the control of gene expression is dictated less by sequences proximal to a gene (e.g., promoters), but rather to enhancer and repressor binding sites much further away—however, any regulatory sequence must reside within an IGD to influence that gene.

“The position of TADs and boundary regions is remarkably stable between cell types or tissues, even displaying evolutionary conservation among species,” stated Max Delbrück Center for Molecular Medicine’s Irene Mota-Gómez and Darío Lulpazh in a recent review. “The disruption of TADs is a prominent mechanism of human disease, leading to aberrant gene expression and causing congenital disease or cancer.”

Karande offers an example of such a link, describing one situation where a mutation created a novel CTCF binding site between two genes within a loop. This caused a second loop to form, altering gene expression and setting up a cancer pathology. “When we disrupted the CTCF site, we basically saw the disease changing,” he continues. “We started seeing a return to the normal situation.”

This, he suggests, is a perfect example of the importance of both function and structure in health and disease. “In this case, what happened was everything was functioning properly, but the structure changed when an additional CTCF site was created, and you saw the original loop bulging at one point,” he notes. It is precisely this type of intervention that Omega is hoping to achieve with their Omega Controllers platform.

As they are expecting to make a series of announcements in 2020, the Omega team is vague on details about their platform, but offer broad indications of how it will work. According to Karande, “First computationally and then empirically, we are able to figure out, within the IGD that is implicated in that particular disease phenotype, where the regulators sit and which regulators you could go at; if CTCF itself, or depending on whether you are up-regulating or down-regulating, hit the enhancers differentially or you can hit a promoter. Or you can do all of it, because these things tend to be additive.”

While the core binding sequence elements of these CTCF sites are conserved across the genome, their flanking sequences and the context in which they sit is cell-type specific,” adds McCauley. “Having mapped that context across the cell types of interest for us in terms of specific diseases, we can target our controllers to specific cell types and have the effect we want to have only in specific tissues.”

The goal is then to use known epigenetic modulators to adjust gene expression in the desired manner, all of which will be encompassed in a yet-to-be-specific delivery system. To this latter aspect, Karande points to the achievements of sibling company Moderna, assured that delivery solutions will be forthcoming.

An additional feature that potentially works in Omega’s favor is the understanding that IGDs also tend to comprise genes functioning within the same metabolic pathways, explains Karande. “The way nature has provided for those genes, those genes are put in the IGD because they tend to be modulated from within the IGD, we are able to differentially modulate these genes.”

Again, without offering specifics, he suggests that in early experiments, the company was able to modulate multiple genes from within an IGD involved in inflammation and immunology, and produced outcomes currently achieved by a multibillion-dollar drug on the market today.

Aside from their own therapeutic plans, Karande sees opportunities to work with other companies to enhance the efficacy of other drugs, either directly by laying the metabolic groundwork. “Think of checkpoint inhibitors, which are miraculous drugs,” he offers. “You have 30 to 40 percent responders, which means 60 to 70 percent of people don’t respond to these drugs.”

“One of the research papers that came out of the Fred Hutchinson Institute earlier this year suggested that when a certain DUX4 gene is expressed in patients who have cancer, I/Os [immuno-oncology therapies] don’t work,” he continues. “If we can go and shut that gene down temporarily—we’re not editing—then we’re not doing anything to the gene except turning it down so that the I/O can act—imagine that when a certain DUX4 gene is up-regulated in 40 to 50 or 60 percent. Imagine what you’re creating, in terms of patient benefit.”

This idea of modulation rather than alteration that causes Karande to describe Omega’s approach as genomic medicine rather than genomic surgery.

Regardless of which approach is followed, most of these gene replacements, editing or modulation therapies remain a few years from clinical trials. Yet, given the complexity of human health and disease, it is nice to know we will likely have options. //

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TACKLING LYSOSOMES. The University of Victoria’s Francis Choy (center), Rhea Ashmead (left) and Chloe Christensen (right) are combining base editing with stem cells to address lysosomal storage diseases like Sanfilippo syndrome (MPS IIIB).

“Bayon Search for more information, visit www.DDN-News.com
When it comes around, March will bring with it the 59th Society of Toxicology (SOT) Annual Meeting and ToxExpo, held this year in Anaheim, Calif. The meeting is expected to include over 6,000 scientists from countries all over the world. DDNews spoke with Ronald N. Hines, SOT president 2019-2020, and George Daston, SOT vice president 2019-2020, to learn what the meeting has in store for its attendees.

“The SOT Annual Meeting and ToxExpo is the largest gathering of toxicologists in the world, featuring more than 2,000 presentations and 80 featured and scientific sessions. We also connect attendees with 300-plus service providers through the ToxExpo and offer hundreds of events designed to foster networking and engagement with colleagues,” says Hines. “As a result, the SOT Annual Meeting is a place where people showcase the best in toxicological research while also sowing the seeds for future research and collaborations. The SOT membership is diverse in its interests and specialties, and the SOT meeting reflects this diversity.”

“As usual, the SOT annual meeting will have many sessions that are highly relevant for scientists who develop or regulate pharmaceucicals,” notes Daston. “This includes sessions on development of protein degradation therapies, relevance of lysosomal dysregulation in adverse responses and predicting adverse effects related to cancer immunotherapy. The meeting will also feature continuing education courses on gene therapy, cancer immunotherapy and options for treatment of ocular diseases.”

Regarding any new features the 2020 meeting may bring, Hines points out, “We are constantly assessing the meeting and its content to ensure that it is fitting the needs and expectations of our attendees. One of the new features we are introducing this year is the TOX Presentation Corner. Located in the ToxExpo Exhibit Hall, this intimate space will feature short, invited presentations designed to provide training on topics such as grant funding, highlight opportunities for career development and transitions, and to foster exchanges of science and ideas."

The TOX Presentation Corner presentations are scheduled to occur during ToxExpo hours (9 a.m. to 4:30 p.m.) from March 16-18. The times and details for each presentation are available in SOT’s Online Planner and in the SOT Event App, which launches in February.

Hines states, “In addition, we have shifted the 2020 Plenary Session … to 1 p.m. on Monday and have adjusted last year’s pilot of 90-minute symposium and workshop sessions to have these shorter sessions occur on each day of the meeting instead of one afternoon.”

This year’s plenary session will be delivered by Atul Butte of the University of California, San Francisco. The presentation, “Precisely Practicing Medicine from 700 Trillion Points of Data,” covers how computing capabilities are expanding our ability to interpret large biomedical research datasets in new and transformative ways.

“To help ensure that the SOT meeting focuses on topics and issues of interest to a global audience, the society has partnerships..."
with other toxicology associations and organizations that result in special sessions during the meeting each year,” adds Hines. “This tradition continues in 2020 with the SOT/EUROTOX Debate on individual toxicity in risk assessment, a symposium session on oxidative stress with the Japanese Society of Toxicology, an award lecture exchange with EUROTOX and the featured Medical Research Council (MRC) lecture by Dame Amanda Fisher on epigenetics and inheritance.”

The SOT/EUROTOX debate, “Individual Toxicity Is the Future of Risk Assessment,” will be debated by Syril D. Pettit of the Health and Environmental Sciences Institute and Alan R. Boobis of Imperial College London. The “Oxidative Stress in Multiple Manifestations of Toxicity” session features speakers Yoshio Kamagai of the University of Tsukuba, Yoshiro Saito of Tohoku University, Alicia R. Timme-Laragy of the University of Massachusetts Amherst, and Dean P. Jones of the Emory University School of Medicine.

“We also are looking forward to a session featuring the new Toxicological Sciences editor-in-chief Jeffrey M. Peters and colleagues speaking about the future of scientific journals, and a tribute to SOT Past President Linda S. Birnbaum in honor of her retirement as NIEHS [National Institute of Environmental Health Sciences] director,” Hines mentions.

The scientific journal session, “NextGen ToxSci: From Journal Improvements to Community Building through Social Media,” also includes Peters’ colleagues Alison Harrill of NIEHS, Dana C. Dolinoy of the University of Michigan School of Public Health, David Crotty of Oxford University Press and Laura Van Winkle of the University of California, Davis. The tribute, entitled “A Career in Advancing the Field of Toxicology,” will include Martin van den Berg of Universiteit Utrecht, Suzanne E. Fenwick and Ron Wooyk of NIEHS.

SOT HONORS AND AWARDS

The awardees will be honored during an awards ceremony on March 15, 2020.

SOT HONORARY MEMBERSHIP
- Laura E. Nagy, Ph.D., Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland
- Susan W. Scott, Ph.D., University of California, San Francisco

SOT ACHIEVEMENT AWARD
- James P. Landy, Ph.D., Michigan State University, East Lansing
- Renee J. Geissler, Ph.D., University of North Carolina at Chapel Hill

SOT AWARD FOR OUTSTANDING LEADERSHIP IN TOXICOLOGY
- Julie A. James, Ph.D., University of Arizona

SOT ENHANCEMENT OF ANIMAL WELFARE AWARD
- Margarita V. Llopis, Ph.D., University of California, Berkeley

SOT FOUNDERS AWARD (FOR OUTSTANDING LEADERSHIP IN TOXICOLOGY)
- Sidney Green, Ph.D., ATS, Howard University College of Medicine, Washington, D.C.

SOT LEADING EDGE IN BASIC SCIENCE AWARD
- Wen-Xing Ding, Ph.D., University of Kansas Medical Center, Kansas City

SOT MERIT AWARD
- Norbert E. Kamiński, Ph.D., Michigan State University, East Lansing

SOT TOXICOLOGIST MENTORING AWARD
- Oliera A. Olivera, Ph.D., ATS, National Cancer Institute, Rockville, Md.

SOT TRANSLATIONAL IMPACT AWARD
- David A. Jett, Ph.D., NIH Countermeasures Against Chemical Threats (CounterACT) Program and National Institute of Neurological Disorders and Stroke, Bethesda, Md.

SOT BRUCE A. FOWLER UNDERGRADUATE EDUCATOR AWARD
- Christine Perdan Curran, Ph.D., Northern Kentucky University, Highland Heights

SOT TOXICOLOGICAL SCIENCES PAPER OF THE YEAR AWARD
- “Comparative Analysis of Zebrafish and Planarian Model Systems for Developmental Neurotoxicity Screens Using an 87-Compound Library.”
  - Danièle Happram, Lisa Truong, Siq Zhang, Robert Tanguay and Eva-Maria S. Collins
Committee on Diversity Initiatives Reunion
Saturday, March 14, 7:30 p.m. to 8:30 p.m.
Chairs: James P. Luyendyk, Michigan State University; and Frederic J. Moulin, U.S. FDA.
Host: Committee on Diversity Initiatives (CDI)
Join the CDI in celebration of the 31st year of the Undergraduate Diversity Program. The CDI Reunion is a great opportunity for former students, organizers and volunteers of the program to gather and celebrate success in encouraging the next generation of scientists. This event will include the presentation of the 2020 Perry J. Gehring Diversity Student Travel Award. Tea, coffee and dessert will be served.

Awards Ceremony
Sunday, March 15, 5:15 p.m. to 6:30 p.m.
The 2020 SOT award recipients are recognized after a pre-ceremony musical performance by Gregg Hawkins. Please join SOT in honoring this year’s awardees.

Welcome Reception
Sunday, March 15, 6:30 p.m. to 7:30 p.m.
Everyone is invited to join SOT for this informal start to the 2020 meeting, an opportunity to renew friendships and make new acquaintances. Hors d’oeuvres and a cash bar are available during this event.

25-Year (or More) Member Reception
Sunday, March 15, 7:00 p.m. to 8:00 p.m.
By Invitation Only
If you have been a member of SOT for 25 years or more, please join your colleagues to celebrate and connect with others who have helped shape the Society. Be sure to wear your anniversary pin.

SOT Mentoring Breakfast
Monday, March 16, 6:15 p.m. to 7:45 p.m.
Ticket Required
Endorser: Education and Career Development Committee
SOT is pleased to host its ninth annual Mentoring Breakfast. The Mentoring Breakfast is for SOT members at any career stage—from students and scholars to senior scientists—who are seeking a mentor. Trained facilitators will lead small-group discussions to determine each individual’s needs and needs in a mentor. Facilitators will use this information to connect the participant with an appropriate mentor after the meeting.

Global Gallery of Toxicology
Monday, March 16, 9:00 a.m. to 4:30 p.m.
Toxicology societies from around the world are invited to participate in the Global Gallery of Toxicology, now in its ninth year. Posters from participating organizations are displayed in a designated area of the Exhibit Hall during ToxExpo hours. These posters showcase the societies’ recent accomplishments, strategic initiatives, and upcoming meetings and opportunities. Meet representatives of the participating organizations at their posters from 2:15 p.m. to 2:45 p.m. on Monday, March 16.

Global Collaboration Coffee
Monday, March 16, 10:30 a.m. to 12:30 p.m.
IUTOX invites all Global Gallery participants and representatives of societies from around the world to the Global Collaboration Coffee, hosted by SOT. This event offers an opportunity for scientific leaders to connect and gain a better understanding of the initiatives of societies around the world. In the afternoon, attendees are encouraged to attend the Global Gallery of Toxicology in the ToxExpo Exhibit Hall, where presenters will share their posters in a representative-attending poster time from 2:15 p.m. to 2:45 p.m. on Monday, March 16.

SOT Pavilion—A Place to Connect
Monday, March 16, to Wednesday, March 18, 9:00 a.m. to 4:30 p.m.
Stop by the SOT Pavilion (Booth #1111) any time during ToxExpo hours to connect and catch up with your SOT friends and colleagues. At the Pavilion, you can also:
• Chat with Toxicological Sciences editor-in-chief Jeffrey M. Peters and managing editor Virginia Hawkins
• Reserve a table or find space for a last-minute meeting with colleagues
• Share Annual Meeting, SOT, and toxicology experiences as part of the Graduate Student Leadership Committee #YouTox campaign
• Learn about SOT activities, programs, and membership

Global Collaboration Coffee
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IUTOX invites all Global Gallery participants and representatives of societies from around the world to the Global Collaboration Coffee, hosted by SOT. This event offers an opportunity for scientific leaders to connect and gain a better understanding of the initiatives of societies around the world. In the afternoon, attendees are encouraged to attend the Global Gallery of Toxicology in the ToxExpo Exhibit Hall, where presenters will share their posters in a representative-attending poster time from 2:15 p.m. to 2:45 p.m. on Monday, March 16.

Research Funding Insights Room
Monday, March 16, 9:30 a.m. to 3:00 p.m.
Tuesday, March 17 - Wednesday, March 18, 9:30 a.m. to 4:30 p.m.
Host: Education and Career Development Committee
Representatives from federal agencies will be available in the Research Funding Insights Room for individual conversations. Make an appointment with a program officer in advance, or check the posted schedule in the Research Funding Insights Room to meet with a staff member who can discuss aspects of scientific review or specific grant opportunities. New investigators are especially encouraged to meet with program staff.

Past Presidents’ 5K Fun Run/Walk
Tuesday, March 17, 6:00 a.m.
Location: TBA
Supported by: IDEXX BioAnalytics
Don’t forget your running shoes, so you can participate in the 10th annual Past Presidents’ 5K Fun Run/Walk. The event is open to anyone, and is a great opportunity to see how many participants and representatives of societies from around the world are invited to participate in the Global Gallery of Toxicology, now in its ninth year. Posters from participating organizations are displayed in a designated area of the Exhibit Hall during ToxExpo hours. These posters showcase the societies’ recent accomplishments, strategic initiatives, and upcoming meetings and opportunities. Meet representatives of the participating organizations at their posters from 2:15 p.m. to 2:45 p.m. on Monday, March 16.

SOT Annual Business Meeting
Tuesday, March 17, 4:45 p.m. to 6:15 p.m.
SOT members are invited and encouraged to attend the Annual Business Meeting. The agenda includes a financial summary, a review of the 2019–2020 accomplishments and highlights of the first-year initiatives of the 2019-2023 Strategic Plan.

Tox ShowDown
Tuesday, March 17, 7:30 p.m. to 9:00 p.m.
Location: TBA
Chair: Philip Wexler, Bethesda, Md.
This is the ninth year of the Tox ShowDown, the toxicological quiz game par excellence. Three teams of three contestants—the Endocrine Disruptors, the Free Radicals and the Toxic Metabolites—battle to answer questions wholly, partially or remotely related to toxicology. Topics run the gamut, including the role of toxicology in history, current events, art, culture, society and science. The event features a cash bar and is a great opportunity to see how many questions you can answer correctly while enjoying a good laugh.

Undergraduate Educator Network Meeting
Date and Time: TBA
Chair: Christine Perdan Curran, Northern Kentucky University
Host: Faculty United for Toxicology
The Undergraduate Educator Network Meeting is for all faculty involved in teaching toxicology to undergraduates, trainees thinking about teaching and those interested in including toxicology at the undergraduate level. Learn about initiatives for undergraduate faculty, provide input, network with colleagues and discuss shared interests.
**BRIEFS**

**So far, so good**

TEL AVIV, Israel—BioLineRx Ltd., working in conjunction with Merck & Co. Inc. (known as MSD outside the United States and Canada), has announced positive results from its triple combination arm of the COMBAT/KEYNOTE-202 study, which is seeking better treatment options for patients with metastatic pancreatic adenocarcinoma (PDAC). This second-line study administered a regimen of BL-8040 in combination with pembrolizumab and a chemotherapy combination of Oxyside, 5FU and leucovorin to patients diagnosed with stage IV PDAC who had failed to see promising long-term results in their first-line treatment approach.

“One of the most difficult cancers to treat, with an extremely poor prognosis upon diagnosis,” says Philip Serfin, CEO of BioLineRx. “These initial results are particularly encouraging in terms of overall response, disease control and durability of responses against the backdrop of a disease indication of PDAC—which is one of the most difficult cancers to treat, with multiple advances give me great confidence that Transgene is well placed to demonstrate and continue the study. The data were presented at ESMO IO 2019.”

**TG4010 to be retired**

**STRASBOURG, France—**A Phase 2 trial of Transgene’s TG4010 in combination with chemotherapy and Odpivo failed to reach its primary endpoint of overall response rate, the company announced last month. The trial was evaluating this regimen as a first-line treatment for patients with advanced nonsquamous non-small cell lung cancer with low-to-no expression of PD-L1. Given the results, Transgene will be halting development of TG4010. Transgene Chairman and CEO Dr. Philippe Archinard said the company was “very disappointed” with the results, but noted that the company is moving forward with other compounds, such as TG4001, TG4010 and TG6002, among others: “These multiple advances give me great confidence that Transgene is well placed to demonstrate and deliver the potential of its novel therapeutic vaccines and oncolytic viruses designed to improve the treatment of solid tumors.”

**ADVM-022 success is no OPTIcal illusion**

Adverum’s wet AMD candidate helps maintain vision in Phase 1 trial

**BY KELSEY KAUSTINEN**

MENLO PARK, Calif.—As 2019 wound to a close, Adverum Biotechnologies Inc. shared data from the first cohort of its Phase 1 OPTIC trial of ADVM-022 in wet age-related macular degeneration (AMD), showing that a single administration can help maintain vision for up to eight months. Adverum presented the data at the Retina Subspecialty Day Program of the American Academy of Ophthalmology (AAO) 2019 Annual Meeting. ADVM-022 consists of a proprietary vector capsid, AAV-7m8, which carries an aflibercept cassette. The therapy is meant to offer long-term efficacy, reduce frequent anti-VEGF injections, improve patient compliance, and to improve vision outcomes.

**Resistance to Alzheimer’s is not futile**

Troriluzole successfully advances past interim futility analysis in pivotal Phase 2/3 study

**BY DDNEWS STAFF**

NEW HAVEN, Conn.—Biohaven Pharmaceutical Holding Co. Ltd., a clinical-stage biopharma company with a portfolio of late-stage product candidates targeting neurological and neuropsychiatric diseases, in December announced successful completion of a preplanned interim futility analysis for the T2 Protect AD Study. This study is an ongoing Phase 2/3 clinical trial of troriluzole in Alzheimer’s disease led by the Alzheimer’s Disease Cooperative Study (ADCS) at the medical school of the University of California, San Diego (UC San Diego).

The independent data safety monitoring board communicated that futility was not met based on prespecified criteria for the interim analysis, which evaluated standard cognitive assessments and hippocampal volume on magnetic resonance imaging parameters. The interim analysis was designed specifically to allow for stopping the trial early due to futility. In order to pass the interim futility analysis, troriluzole had to demonstrate numerically greater benefit over placebo on at least one of the two prespecified criteria at 26 weeks, either

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**ADVM-022 is a therapy meant to offer long-term efficacy, reduce frequent anti-VEGF injections, improve patient compliance, and to improve vision outcomes for patients with wet AMD and diabetic retinopathy.**

**ADVM-022 CONTINUED ON PAGE 24**

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**BIOHAVEN CONTINUED ON PAGE 24**
TRIPLE

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chemokine receptor known to be over-expressed in many human cancers, including PDAC. CXCR4 plays a key role in tumor growth, invasion, angiogenesis, metastasis and therapeutic resistance, and CXCR4 overexpression has been shown to be correlated with poor prognosis. Adding BL-8040 shows a tolerable safety profile which compares favorably with that of the individual components alone. The overall response rate of 32 percent, coupled with a 77 percent disease control rate, is a substantial improvement to the current second-line chemotherapy standard of care, which reports 17 percent and 52 percent, respectively.

“Metastatic pancreatic cancer has a very poor response to chemotherapy, and immunotherapy treatments have failed to show any effect as single agents,” explained Dr. Manuel Hidalgo, principal investigator of this study and chief of the Division of Hematology and Medical Oncology and a senior member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine and New York-Presbyterian/Weill Cornell Medical Center. “These promising initial results presented today show an overall response rate almost double the current chemotherapy standard-of-care treatment in second-line patients. The results are even stronger when taking into account the extended durability of clinical benefit seen to date in this study (median of 7.8 months), compared to approximately three months of response duration with other treatments for second-line pancreatic cancer. I look forward to the survival data expected in mid-2020.”

The durability of the results is of particular interest, with highly anticipated progression-free survival data. While the current length of the study does not allow for firm data, the researchers are bullish based on the few patients now approaching a full year of treatment who are responding and experiencing a mild enough toxicity to keep them in the study. Approximately 10 percent of patients experience a grade 3/4 toxicity, which is in line with other treatment modules.

“We are very excited by the positive data accumulating from this triple combination arm of our Phase 2a pancreatic study under our collaboration with Merck,” Serlin remarked. “These data continue to confirm our hypothesis relating to the synergistic effect of cytotoxic chemotherapy, along with the trafficking, tumor microenvironment modulation and T cell infiltration effects seen in PDAC patients from previous dual combination trials of BL-8040 with checkpoint inhibitors. It is therefore very encouraging to see robust and durable responses to the triple combination treatment, especially as we continue to see a trend of patients receiving treatment for an extended period that move from stable disease to partial response. We hope to see these results translate into an extended survival benefit for these patients, which we expect to announce in mid-2020, and we hope will pave the way for use of immunotherapy in pancreatic cancer and in other cold tumors.”

BioLineRx intends to initiate conversations with regulatory agencies in early 2020 to reach an agreement about the fastest and most efficient route to expand clinical trials for this triple-arm approach. In addition, BioLineRx is exploring other applications for BL-8040, which is also being evaluated in a Phase 2b study in consolidation acute myeloid leukemia and a Phase 3 study in stem cell mobilization for autologous bone-marrow transplantation. The company also has an ongoing collaboration agreement with Genentech, a member of the Roche Group, to evaluate BL-8040 in combination with Genentech’s atezolizumab in two Phase 1b/2 solid tumor studies.
**BIOHAVEN**

**CONTINUED FROM PAGE 22**

cognitive function as measured by the ADAS-cog and hippocampal volume assessed by magnetic resonance imaging. Biohaven announced that based upon the interim futility and safety analy-
sis that the study would continue.

“Given the tremendous bur-
den of Alzheimer’s disease on patients and families, as well as public health, it is imperative that we rapidly conclude and end UTNT study promising new treat-
ments such as troriluzole,” said Dr. Howard Feldman, director of the ADCS and a professor of neurosciences at the UC San Diego School of Medicine, who is principal investigator of the T2 Protect AD Study. “We are very pleased to see that the promising ana-
sis supports continuation of the T2 Protect AD Study, and we are hopeful that the trial will demon-
strate a meaningful benefit of troril-
zole ameliorates the symptoms of Alzheimer’s disease.”

Troriluzole is an oral, once-
daily tablet that modulates glu-
tamates and is being evaluated as a symptomatic treatment for mild-to-moderate Alzheimer’s disease. The trial is a Phase 2/3 randomized, double-blind, placebo-controlled study evalu-
ing the efficacy and safety of troriluzole in patients diag-
osed with Alzheimer’s disease of mild-to-moderate severity (Mini-Mental State Examina-
tion score of 14-24). Patients are randomized on a 1:1 basis to receive 280 mg of troriluzole or placebo once daily for 48 weeks. The trial is being conducted in collaboration with the ADCS at University of California San Diego School of Medicine.

Noted Dr. Vlad Coric, CEO of Biohaven: “We are encouraged by advancing past the prespecified futility criteria after the first 100 patients, allowing us to move forward with treatment and we look forward to full results upon study comple-
tion. This is an important mile-
stone twice-daily and placebo-
open ment program as troriluzole continues to be studied in four pivotal Phase 2/3 trials evaluating its efficacy in multiple neurologic and neuropsychiatric disorders.”

EDITCONNECT: E012018

**ORMD-0801**

**CONTINUED FROM PAGE 1**

insulin candidate in individuals with type 2 diabetes and inade-
quate glycemic control on oral antihyperglycemic agents. A reduction in AIC at week 12 was the primary efficacy endpoint, with various safety endpoints also being evaluated. Should ORM-0801 continue to be successful in the clinic, it could be used to commercialized oral insulin capsule treatment for diabetes.

“This Phase 2b study provides statistically significant efficacy data,” said Dr. Joel Neutel, co-director of the University of California San Diego School of Medicine.

“Oral delivery of insulin has the potential to represent a significant advance for patients with wet AMD. It is very encouraging that there continues to be zero rescue injections in this cohort of treat-
ment-naive patients with more than six months follow-up on all patients . . . We look forward to being able to deliver this novel intravitreal gene therapy candidate as soon as possible to patients with wet AMD and diabetic retinopathy, our second indication for ADVM-022. We are grateful for all of the investi-

ators, patients and care-
givers who continue to participate in the OPTIC trial,” said Aaron Nordiak, chief medical officer of Adverum.

In terms of upcoming milestones for the OPTIC trial, enrollment for the fourth cohort is slated to begin in 2020, with 24-week data from the first cohort and 24-week data from the second cohort to be presented in the first half of 2020. Adverum also intends to submit an Investigational New Drug (IND) applica-
tion for ADVM-022 for the treat-
ment of diabetic retinopathy in H1 2020.s

**ADVM-002**

**CONTINUED FROM PAGE 22**

for patients with wet AMD and dia-
betic retinopathy.

Wet AMD is an aggressive form of age-related macular degenera-
tion in which abnormal blood ves-
sels grow underneath and into the retina, and then leak fluid and blood into and beneath the retina, leading to vision loss. At present, the stan-
dard of care for treating wet AMD is anti-VEGF intravitreal injections every four to eight weeks, and the accu-


The California Retina Research Consultants is a non-profit research organization that conducts clinical trials for new treatments in ophthalmology. The California Retina Consultants is one of the largest private clinical research organizations for ophthalmology in the United States. The California Retina Consultants is dedicated to advancing the treatment of eye disease through clinical research and education.

**ADVM-022**

**CONTINUED FROM PAGE 22**

The OPTIC Phase 1 trial is a mul-
ticenter, open-label trial evaluat-
ing the safety and tolerability of a single intravitreal (IVT) adminis-
tration of ADVM-022 in patients with wet AMD who are respon-
sive to anti-vascular endothelial growth factor (VEGF) treatment. The primary endpoint of the trial is the safety and tolerability of this treatment regimen, with second-

ary endpoints including change in best-corrected visual acuity, change in central subfield thick-
ness and macular volume, mean number of anti-VEGF rescue injec-
tions and percentage of patients needing anti-VEGF rescue injec-
tion. Each patient will be followed for two years.

The first and second cohorts con-
sist of six patients each, with the third and fourth cohorts consist-
ing of nine patients each. Adverum

**An intravitreal gene therapy that can significantly reduce the number of injections required to maintain vision would be welcomed by patients with wet AMD as well as their caregivers and physicians.”**

Dr. Dante Pieramici, co-director of the California Retina Research Foundation

“The clinical profile of ADVM-
022 demonstrates this gene ther-
apy’s potential to be a significant advance for patients with wet AMD. It is very encouraging that there continues to be zero rescue injections in this cohort of treat-
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**EDITCONNECT: E012017**

**Biohaven has decided it will continue its ongoing Phase 2/3 clinical trial of troriluzole in Alzheimer’s disease now that the investigational compound has completed a preplanned interim futility analysis.**

Injection has been the traditional way of administering insulin for decades, but Oramed seeks to change that with investigational oral insulin ORM-0801. Reduction in their mean AIC of 0.60 percent from baseline, or a reduction of 0.54 percent when adjusted for placebo—a clin-
ically meaningful improvement in glucose control. No serious drug-related adverse events were reported, and there was no noted weight gain or increase in the frequency of hypoglycemic episodes.

During an investor event to discuss the Phase 2b results, Dr. Ramachandra Naik, Professor of Medicine/Endocrinology at SUNY Upstate Medical Univer-
sity, noted that the results show ORM-0801 could serve as a second-, third- or fourth-line oral agent for individuals with diabetes, with Dr. Joel Neutel, principal investigator of the study and director of Research at Orange County Research Center, adding that the compound is also capable of being administered alongside other glucose-lowering agents. According to Naik, patients taking more than one antihyperglycemic agent points to a more advanced stage of dis-


“Doc, how many and for how long?” said Dr. Dante Pieramici, co-director of the California Retina Research Foundation, managing partner of The California Retina Consultants and investigator in the OPTIC trial, said, “An intravitreal gene therapy that can significantly reduce the number of injections required to maintain vision would be wel-
comed by patients with wet AMD as well as their caregivers and physicians. I’m encouraged by the recently presented clinical data from the first cohort of the OPTIC trial showing that the therapy was safe and well tolerated with no res-
cue injections required in patients who previously required frequent anti-VEGF injections to control their wet AMD”.

The OPTIC Phase 1 trial is a mul-
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ing the safety and tolerability of a single intravitreal (IVT) adminis-
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Companies ink agreement to develop rapid, point-of-care solution for diagnosing bloodstream infections

BY KELSEY KAUSTINEN
SANTA CRUZ, Calif. & NEWCASTLE UPON TYNE, U.K.—According to the World Health Organization, more than 30 million people worldwide develop sepsis each year, about six million of whom eventually die from the infection. Treatment consists of broad-spectrum antibiotics, but this approach sometimes proves ineffective if a patient has resistance to any of the drugs, and it also further contributes to the issue of antibiotic resistance. In hopes of addressing this issue, Ontera Inc. and QuantuMDx Group Ltd. have launched a collaboration for the development of a next-generation solution for bloodstream infection and drug resistance detection.

“Today, 30 percent of patients receive inappropriate antimicrobial therapy. By not only identifying sepsis but also resistance to most common antibiotics in less than 30 minutes, we will transform the sepsis landscape and impact lives,” said Murielle Thinard McLane, president and CEO of Ontera. “We have set out on a mission to democratize access to molecular information to create a more sustainable planet. This collaboration with QuantuMDx is a major proof point along that mission.”

QuantuMDx and Ontera both bring strong bacteria-focused platforms to this agreement. QuantuMDx’s Capture-XT technology captures, concentrates and enriches target pathogens from as little as 3 ml of blood for quick visual diagnosis. This platform also enables downstream utilization such as drug-susceptibility analysis, PCR, next-generation sequencing and, thanks to the combination with Ontera’s technology, nanopore detection.

For its part, Ontera’s sample-to-answer (SAM) NanoDetector platform can quickly amplify multiple bacterial targets to differentiate between antibiotic-resistant and susceptible strains of bacteria. By using silicon nanopore, the platform can quantitatively measure nucleic acids, proteins and small molecules within minutes. Dr. Trevor J. Morin, chief scientific officer at Ontera, tells DDNews that Ontera’s responsibility under this agreement will be to develop a system that will provide accurate results within seconds.

Ontera and QuantuMDx have joined forces in a collaboration that aims to unite their respective platforms to develop an integrated option for rapid, point-of-care sepsis diagnosis. Pictured here is Ontera’s SAM technology.

Cologuard mechanism tested for liver cancer

Test that has proven useful for non-invasive colorectal cancer screening leads to new possibilities

BY KRISTEN SMITH
MADISON, Wis.—Exact Sciences Corp., the company behind the popular non-invasive colorectal cancer screening test Cologuard, has focused on a similar approach to identify a new mechanism to test for the most common type of liver cancer: hepatocellular carcinoma (HCC).

Cologuard successfully utilizes methylated DNA biomarkers to detect colorectal cancer. But Exact Sciences has also focused on the challenge of detecting liver cancer.

The company’s approach is non-invasive, which means patients do not need to undergo a colonoscopy. The company’s technology amplifies multiple bacterial targets to differentiate between antibiotic-resistant and susceptible strains of bacteria. By using silicon nanopore, the platform can quantitatively measure nucleic acids, proteins and small molecules within minutes. Dr. Trevor J. Morin, chief scientific officer at Ontera, tells DDNews that Ontera’s responsibility under this agreement will be to develop a system that will provide accurate results within seconds.

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to establish the best partnership to fund the integration of Ontera’s and QuantuMDx’s technologies into an integrated platform. He notes that “To date, the two companies have already conducted a feasibility study.”

“Ontera is a mission to accelerate access to precise biological information at the point of need. And QuantuMDx’s mission is marked by making transformative, quality diagnostic technologies accessible to everyone, so that diseases can be detected and treated earlier, and transmission eradicated,” says Morin. “This partnership plays to the strengths of both companies’ unique technologies: QuantuMDx’s ability to conduct highly sensitive, yet cost-effective, moderate multiplexed testing while Ontera’s ability to differentiate between live and dead bugs. Partnering these two technologies allows us to target complex infectious areas where the current diagnostic solution is culturing or sequencing.”

“This partnership to develop a new tool for the diagnosis of sepsis underscores how we’re using solutions by providing caregivers and patients fast access to precise diagnostic information to ensure the best and most appropriate treatment,” he adds.

“Sepsis is one of the hardest diseases to detect. It’s like looking for a needle in a haystack, due to the low concentration of organisms in the blood stream that cause disease,” remarked Jonathan O’Halloran, chief scientific officer at QuantuMDx. “Our early prototype testing has already shown sensitivity in the range required for this kind of test and performed in minutes from spiked bacteria in whole blood. We haven’t even pushed the technology yet, but it has the potential to become a paradigm-shifting, powerful device. And, by including drug resistance in the assay to enable right first-time prescribing, the impact of this partnership could be profound.”

According to Morin, Capture-XT will be used by Exact to develop “an accurate, affordable and integrated platform which detects bloodstream infections rapidly at the point of need.” The SAM platform is a “highly sensitive and specific platform that can interrogate up to 20 targets simultaneously, including nucleic acids, proteins and small molecules, all in the same assay,” Morin explains, and offers multi-modal analysis at point of care in under 20 minutes. One of the advantages that the platform also has diagnostic applications in areas such as STI panels, Resp panels and gastrointestinal panels.”

**EXACT CONTINUED FROM PAGE 25**

(MDUs), leading the scientists to explore whether the same class of biomarkers could be detected in blood and represent an important advancement in liquid biopsy for detecting HCC.

They documented extremely promising results by examining 443 patients, including 135 HCC cases and 308 age-matched and liver disease etiology-matched controls. The test demonstrated 80-percent sensitivity at 90-percent specificity with a novel combination of six blood-based biomarkers for HCC. The study also showed 71-percent sensitivity for early-stage HCC at 90-percent specificity. These results were compared to the current standard test of the alpha-fetoprotein (AFP) test, which demonstrated 45-percent sensitivity at 90-percent specificity for early-stage HCC. The findings were presented at the 2019 annual meeting for the American Association for the Study of Liver Diseases (AASLD) in Boston.

“When cancer is in its earliest stages in asymptomatic individuals, it can be the most difficult to detect through biomarker screening because of the natural history of early tumor development and cancer biology; targeted biomarkers may only be present in peripheral blood in very small amounts,” explained Scott Johnson, senior vice president of research and development at Exact Sciences. “Detecting individual or groups of biomarkers in very small concentrations challenges fundamental requirements for balancing the sensitivity and specificity of individual or panels of biomarkers. We have made progress with these challenges through improved methods of stabilization and purification of cell-free DNA from blood, as well by developing optimized, highly sensitive methods for interrogating methylated DNA. With specificity set at 90 percent, our novel combination of six blood-based biomarkers (four MDUs and two proteins) for HCC detection demonstrated 80-percent overall sensitivity, with 71-percent sensitivity for early-stage cancer (Barcelona Clinic Liver Cancer stages 0 and a1).”

The test has been recognized as a Breakthrough Device by the U.S. Food and Drug Administration, and correspondingly is included in the Exact Sciences Breakthrough Devices program, which expedites development, assessment and review processes to provide patients and healthcare providers with timely access to new technologies.

**TODOS CONTINUED FROM PAGE 25**

A clinical study in 2018, Lympro PET 1, found a significant relationship between LymPro test results and amyloid PET imaging in diagnosis of Alzheimer’s Disease. Now, a new trial, Lympro PET 2, seeks to confirm those results.

Dr. Herman Weiss, president of Todos Medical, says, “LymPro is a unique, immune system-based Alzheimer’s blood test. LymPro could prove to be a major breakthrough for Alzheimer’s disease diagnosis by measuring cell cycle disruption and amyloid together, conveniently as part of a blood workup in routine clinical practice. The therapeutic field in Alzheimer’s has begun to see some renewed hope based upon recent gene therapy breakthroughs announced by Biogen that is directly related to the amyloid hypothesis, as well as conditional approval by the National Medical Products Administration (NMPA) in China for the first new Alzheimer’s drug in over 20 years, called Olignan, from Shanghai Green Valley Pharmaceuticals, that is based on gut-brain biology of the microbiome and its effects on the immune system.”

He added, “We believe this renewed optimism and broadening of pathophysiological hypotheses relevant to Alzheimer’s disease being evaluated in the clinic significantly increases the scope for LymPro pharma services collaborations and begins to refine LymPro’s clinical utility profile for primary care physicians as strategies to correct cell cycle dysregulation emerge.”

Todos has developed two cancer screening tests based on TBIAs (Todos Biochemical Infrared Analyses), a method for cancer screening using peripheral blood analysis. The TBIAs screening method is based on the cancer’s influence on the immune system, which triggers biochemical changes in peripheral blood mononuclear cells and plasma. This proprietary and patented method incorporates biochemistry, physics and signal processing. The company’s two cancer screening tests, Todos Biochemical Infrared for Men (TBIA-M) and Todos Biochemical Infrared for Women (TBIA-W), have received the CE mark.

Amarantus’ subsidiary, Elto Pharma Inc., has development rights to eltoprazine, a Phase Ib-ready small molecule indicated for Parkinson’s disease levodopa-induced dyskinesia, Alzheimer’s aggression and adult attention deficit hyperactivity noted Kevin Conroy, chairman and CEO of Exact Sciences. “A more sensitive and convenient blood-based test could help catch the disease earlier, which may lead to better outcomes. We are encouraged by the data presented [at AASLD], as it shows an important advancement over the options currently available.”

These results are particularly compelling because Exact Sciences researchers are confident that methylated DNA biomarkers can be used to create similar sets of markers for several types of cancers. “We are looking at interventions across the cancer continuum for early-stage HCC at 90-percent specificity with a novel combination of six blood-based biomarkers for HCC and biomarkers and algorithm to provide an effective tool for helping detect HCC earlier in patients who are at risk of developing the disease. We plan to make this tool available in the second half of 2020 and expect to generate real-world evidence to support reimbursement and adoption of the test over time.”

Current guidelines encourage patients to undergo mammogram sound testing, with or without the AFP blood test twice per year. While one’s three-year survival rate nearly doubles for those who undergo regular testing compared to those who do not, fewer than one-third of patients adhere to current guidelines.

“A growing number of patients around the world are considering high risk for developing HCC,” todoss Medical and Amarantus have formed a joint subsidiary, Breakthrough Diagnostics, for research into Alzheimer’s disease diagnostics. disorder. Another Amarantus subsidiary, Cutanogen Corp., is preparing for pivotal studies with Exipell Skin Institute for the treatment of pediatric life-threatening severe burns. ESS is a regenerative medicine-based, autologous full-thickness skin graft technology originally developed by the Shriner’s Hospital that can be used to treat severe burns, as well as several other degenerative dermatological indications. Another subsidiary, MANF Therapeutics Inc., owns key intellectual property rights and licenses related to the development of the therapeutically protein known as mesenchymal stromal cells and platelet derived growth factor (PDGF). MANF Therapeutics is developing MANF-based products as treatments for ophthalmological disorders such as Wolfram syndrome, a metabolic disorder indicated for Parkinson’s disease levodopa-induced dyskinesia, and glaucoma, as well as neuregenerative diseases such as Parkinson’s disease.

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BRIEFS

A preclinical expansion
HAMPTON, N.J.—Late last year, Genesis Drug Discovery & Development (GDD), a member of Genesis Biotechnology Group (GBG), announced the acquisition of the contract research organization New England Discovery Partners (NEDP). The transaction is expected to expand GDD’s preclinical drug research and discovery offerings by enabling the company to provide integrated, single point-of-contact services through the lifetime of a project; streamline all discovery phases; and accelerate projects from discovery through preclinical development.

“We’re committed to building an industry-leading, fully integrated drug discovery CRO,” noted Dr. Eli Meredchai, CEO of GBG. “Adding NEDP is another way to differentiate our capabilities in the early drug discovery space. We’re significantly enhancing our portfolio around organic and medical chemistry to better serve our industry partners.”

Antibody offerings
CAMBRIDGE, U.K.—The 11th Annual Protein & Antibody Engineering Summit, held late last year, saw Abzena showcase its Discovery and Development Services. The company’s Discovery Service uses murine immunization to generate antibodies with high affinity and desired functional properties, an offering that is integrated with full Development Services to evaluate characteristics such as specificity, functionality, safety and manufacturability to increase the chances of clinical success.

Dr. Campbell Bunce, chief scientific officer at Abzena, said: “The development of biologics takes time, is expensive and subject to safety, functionality, stability and scalability liabilities. Having worked with hundreds of drug candidates, Abzena’s Discovery and Development Services offer a defined approach that applies our expertise to guide the discovery and selection of the best drug candidates and reduce the risks that can significantly impact the time and cost typically associated with biopharmaceuticals.”

Cresset Discovery Services contracted by PhoreMost to work on oncology protein target
BY JEFFREY SOULEY
CAMBRIDGE, U.K.—In December, Cresset Discovery Services, a provider of contract research services for early-phase discovery, announced that it had been contracted by PhoreMost Ltd., a UK-based biopharmaceutical company dedicated to tackling “undruggable” disease targets, to work on a novel oncology protein target.

PhoreMost reports that it has leveraged its proprietary SITESEEKER drug discovery platform and PROTEIN libraries to identify a peptide sequence inhibiting a novel protein target that was previously thought to be undruggable, which it says is “relevant to an oncogenic cellular pathway.” Cresset Discovery Services has been contracted under a flexible service agreement to determine how the peptide binds to the target, and to ultimately help find small molecules that have the same effect.

“We have already completed a computational analysis of the peptide sequence to predict binding mode and geometry, using a pre-release version of our Flare V3 software, a structure-based design solution, to provide electrostatic and surface hotspot mapping,” said Dr Martin Slater, director of consulting services at Cresset Discovery Services.

“Drugging the undruggable

This despite challenges of increasingly complex drug production, says GlobalData
BY DDNEWS STAFF
LONDON—The dose-manufacturing-focused market for contract manufacturing organizations (CMOs) in 2018 grew 6.4 percent from its 2017 value. This growth rate is a return to the 7.5 percent to 7 percent year-on-year rate observed in the market in the five years from 2010 to 2014, and is the highest year-on-year growth rate since 2012, according to GlobalData. Moreover, private equity has shown a continued interest in the dose CMO industry, the company says.

Three acquisitions of dose CMOs by private equity firms occurred in 2018, similar to the average number of yearly private equity firm acquisitions across the 2013 to 2017 period, which was 3.4 acquisitions per year. Despite the changing nature of medicines and challenges to the dose CMO industry, it is still perceived as lucrative by investors, says GlobalData.

These insights come out of one of the company’s latest reports, “PharmSource—Contract Dose Manufacturing Industry By The Numbers: Composition, Size, Market Share And Outlook.”

Another takeaway point from the report is that as biologics become increasingly approved and utilized, injectables will be used more often. However, these are more difficult to manufacture while retaining sterility, which requires techniques such as terminal sterilization, aseptic filtration and aseptic formulation. Most injectable oncology drugs will also require containment for manufacture. These require expensive specialist offerings and expertise that not every CMO will be able to perform.

“Drugging the undruggable

Dose CMO industry performing strongly

“As drug production becomes increasingly complex from a molecular and regulatory standpoint, innovative CMOs stand to prosper.”

Adam Bradbury, an analyst at GlobalData

“As drug production becomes increasingly complex from a molecular and regulatory standpoint, innovative CMOs stand to prosper,” said Adam Bradbury, a Pharma analyst at GlobalData.

“...this is especially true as the drug pipeline favors the development of high potency active pharmaceutical ingredients for oncology, where the facilities, expertise and equipment related to their manufacture are prohibitively expensive for smaller pharma companies.”

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End of the road
Illumina and Pacific Biosciences announce termination of merger agreement

BY JEFFREY BOULEY
SAN DIEGO & MENLO PARK, Calif.—A $1.2-billion merger and acquisition (M&A) deal between Illumina Inc. and Pacific Biosciences of California Inc. is officially off the table, as the two parties announced late last year that they “have mutually agreed to terminate their merger agreement” that had been initially announced on Nov. 1, 2018. As noted in a news release about the termination decision, the lengthy regulatory approval process the transaction had already been subjected to and continued uncertainty around the ultimate outcome moved them to scuttle the deal, and now Illumina will pay Pacific Biosciences a termination fee of $58 million.

Things started to look bad in June 2019, when the UK Competition and Markets Authority (CMA) went into the second phase of an investigation into whether to block the M&A and Illumina pushed back the expected closing date for the deal. Then in October, Illumina and Pacific Biosciences announced the completion of a new deal with the former providing $2 billion for the latter.

The deal initially called for the Illumina purchase of Pacific Biosciences. However, as reported by Business & Stragetic/Licensing in this issue, the deal was scuttled after the CMA noted concerns over the merged company’s control of DNA sequencing technologies, and the company was reportedly considering a buyout offer for Pacific Biosciences to put the deal back on track. But after the buyout offer failed to materialize, Illumina and Pacific Biosciences announced the termination of the agreement, which was added to the list of major deals that fell apart in 2019.

End continued on page 29

EXPEDEON AND ABCAM CLOSE TRANSACTION
With deal sealed, Expeodon changes name and shifts to DNA manufacturing and enzymes for diagnostics

BY DDNEWS STAFF
HEIDELBERG, Germany & CAMBRIDGE, U.K.—Expeodon AG recently announced the closing of an agreement with Abcam plc for the sale of Expeodon’s proteomics and immunology business, as announced on Nov. 11, 2019, and as approved by the extraordinary shareholder meeting held a little over a month later. The closing triggers a payment of €120 million by Abcam to Expeodon. Consequently, Expeodon AG also moved to change its company name to 4basebio AG.

“We are now commencing a new chapter in the company’s development with a new name, a new business focus and excellent funding resulting from this transaction. Referring to the four base building blocks of all genetic material, the new company name 4basebio AG reflects our new DNA-based business focus. We will also continue with our successful buy-and-build strategy,” said Dr. Heikki Lanckriet, CEO of the company.

Under its future name 4basebio, Expeodon will focus activities in the field of genomics, building on the expertise in its Spanish business unit, Expeodon S.L.U. in Madrid. The company will focus on DNA manufacturing to supply DNA products for therapeutic and other uses requiring large amounts of high-purity DNA, such as the fast-growing market of novel gene therapies and gene vaccines.

Reportedly, the high need for DNA caused by wide adoption of gene therapies and gene vaccines will likely drive the synthetic biology market to $38.7 billion by 2020, with a compound annual growth rate of 44.2 percent. Besides DNA manufacturing, 4basebio aims to provide research and diagnostic products based on its RNA reverse transcriptase, DNA polymerase and DNA primase enzymes, addressing the research tools and diagnostic products markets.

“We are now commencing a new chapter in the company’s development with a new name, a new business focus and excellent funding resulting from this transaction. Referring to the four base building blocks of all genetic material, the new company name 4basebio AG reflects our new DNA-based business focus.”

Dr. Heikki Lanckriet, CEO of Expeodon (4basebio)
Yseop and Litera partner up to help life-sciences companies

BY DDNEWS STAFF

PARIS—Yseop, an artificial intelligence (AI) software company that considers itself a pioneer in natural language generation (NLG), has announced a strategic partnership with Litera, a supplier of document processing technology. The partnership brings together two complementary service offerings to empower life-sciences companies with solutions for more efficient and effective management of regulatory compliance processes.

As the companies note, bringing a new drug to market takes between 10 and 15 years and costs between $1.5 billion and $2 billion, adding, “in a context of heightened regulatory scrutiny and obligations, relying on manual reporting systems and complex, resource-intensive and time-consuming processes, can jeopardize the whole investment.”

Litera is committed to accelerating the creation, review, formatting and standardization of documents to offer the fastest path to compliance, with a dedicated offering for regulatory, medical affairs and clinical operations specialists. Its solution portfolio (DocXtools for Life Sciences, Change-Pro Premier and Content Companion) offers, the company says, a best-of-breed combination to streamline and accelerate high-quality submissions.

“Patients are waiting. This is the most important driving factor we bear in mind when working with life-sciences companies,” said Matt Miller, Litera’s director of product management. “We are always looking for technologies that can help them complete submissions faster. Yseop’s expertise in AI-powered intelligent automation blends in well with our document processing technology, and we are proud to be able to work collaboratively on offering the best approach to streamline regulatory submissions.”

Working closely with some leading global leading pharma, Yseop has developed a specialized expertise in providing automated reporting solutions for medical writers, built on advanced NLG technology. By automating some of the data-heavy and time-consuming manual reporting sections needed to ensure compliance and safety, Yseop’s NLG solution aims to help pharmaceutical companies save significant time and money and get drugs to market faster, with the company’s CEO, Emmanuel Walckenaer, noting, “NLG offers this unique ability to help scale human expertise, and regulatory submission is one of the areas where the benefits it delivers proves the more valuable.”

Emmanuel Walckenaer, CEO of Yseop

“NLG offers this unique ability to help scale human expertise, and regulatory submission is one of the areas where the benefits it delivers proves the more valuable.”

Emerging from the United States and the United Kingdom ultimately viewed a proposed merger between Illumina and Pacific Biosciences as a threat to competition, and their opposition ultimately caused the two companies to scuttle the deal recently.

“We are disappointed that our customers and other stakeholders will not realize the powerful advantages of integrating the sequencing capabilities of our two companies. With that said, we are confident in the future of Pacific Biosciences.”

Michael Hunkapiller, CEO of Pacific Biosciences

adding, “We are disappointed that our customers and other stakeholders will not realize the powerful advantages of integrating the sequencing capabilities of our two companies. With that said, we are confident in the future of Pacific Biosciences as we continue to pursue improved sequencing accuracy and throughput that can be utilized in an ever-expanding number of applications.”

Analysts seem largely unfazed by the outcome, with PiperJaffray’s William Quirk echoing Hunkapiller’s optimism in an analyst note that said, in part, “We continue to believe the Sequel II launch is going well, with strong placements the first two full quarters of the launch. A distribution partnership with Illumina could also drive further adoption of PacBio tech. We believe PacBio standalone is worth more now than when the deal was announced.”

Likewise, there doesn’t seem to be much worry for Illumina’s future in the wake of the deal’s collapse.

For example, Evercore ISI analyst Vijay Kumar wrote that the M&A deal was “not key to Illumina’s growth story ... Thus, the news is more noise than substance in our minds” and, if anything, removes the risk of potential dilution from the transaction, Kumar added.

A note from SVB Leerink written by Puneet Souda and colleagues predicted that the life-sciences and other research markets would lose out more than Illumina, saying that “While it is disappointing that the deal will not go through, we see limited to no impact to ILMN [Ilumina]. Combining the short-read + long-read sequencing data would have been a positive for the industry and the sequencing end-market as a whole — as it would have unleashed applications not accessible today or given access to regions of genomes that are refractory to either technologies.

“We believe the long-term growth trajectory for ILMN remains intact, even without PacBio, and ILMN holds potential to pursue other avenues for long-read sequencing including building the capability internally.”

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CMA’s provisional findings said that the deal would lessen competition in the next-generation sequencing (NGS) market in the United Kingdom and so it might indeed block the deal—news that was followed in December by word that the U.S. Federal Trade Commission had filed an administrative complaint alleging Illumina was seeking to unlawfully maintain a monopoly in the NGS market in the United States.

Both companies publicly expressed their disappointment, with Francis deSouza, president and CEO of Illumina, saying, “We believe this proposed combination would have broadened access to Pacific Biosciences sequencing technology, significantly expanded and accelerated innovation and ultimately increased the clinical utility and impact of sequencing,” and Dr. Michael Hunkapiller, CEO of Pacific Biosciences, adding, “In a context of heightened regulatory compliance processes.

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The lack of interoperability between different vendors’ instruments and software has traditionally presented a barrier to laboratories adopting the solutions that best meet the unique needs of their workflows,” said Matt Hazlewood, senior director, global enterprise chromatography data systems for Thermo Fisher Scientific. "The renewal of our commitment with Agilent for mutual compatibility and third-party control of instruments allows customers to have continued access to our market-leading Chromelon CDS software platform, and deploy the analytical solutions they need without compromising the flexibility or efficiency of their workflows.”

Addled John Sadler, vice president and general manager, software and informatics for Agilent: “Agilent’s open systems approach to laboratory informatics allows customers to select the best hardware and software for their needs. That is why we invest in integrating third-party analytical instruments into our OpenLab software suite in collaboration with other analytical instrument manufacturers—our aim is to provide simple and complete support for our mutual customers.”

Incubation monitoring system to improve the regenerative medicine workflow

WALTHAM, Mass.—From the Olympus Life Sciences Business comes the Provi CM20 monitoring system, which provides quantitative data about the health of cell cultures while they are in the incubator. The system periodically scans the cultures, counts the number of cells, determines confluency and wirelessly communicates the data to a tablet or desktop computer. By using the CM20 system, researchers reportedly can acquire data that will help improve the reproducibility and stability of their cell culture process.

San Jose, Calif.—Thermo Fisher Scientific and Agilent Technologies announced recently that they are continuing their agreement to the industry-wide Instrument Control Exchange Program (ICEP), fostering compatibility among key vendors’ instrumentation and chromatography data systems (CDS). Organizations across the life sciences and applied industries will, the companies say, continue to benefit from the ability to select the hardware and software that most appropriately meets their application and business needs through the sustained involvement of key vendors.

Marking a significant step forward in the 15-year history of the ICEP, the latest enhancements to Thermo Scientific Chromelom CDS software allow users to streamline quality control workflows through improved compatibility with Agilent’s gas chromatography and high-performance liquid chromatography instrumentation. Additionally, for the first time, Thermo Fisher’s GC, HPLC and selected ion chromatography instruments can also be controlled in Agilent’s OpenLab CDS. This allows users to increase workflow flexibility and efficiency through the implementation of instruments suited to their needs.

"Working with Dr. Julien Michel at the University of Edinburgh UK, an expert in free energy methods, we combined and enhanced open-source tools to generate a robust, user-friendly, validated and accessible implementation of FEP,” commented Dr. Mark Mackey, chief scientific officer at Cresset. “This enables computational chemists to predict the activities of new molecules during drug discovery, significantly reducing synthetic chemistry costs and improving the time to clinical candidate.”

PromoCell now offers in-vitro disease models

HEIDELBERG, Germany—PromoCell, a manufacturer of human primary cells and cell culture products, now offers cell disease models covering a wide range of diseases, including diabetes type 1 and 2, respiratory diseases such as chronic obstructive pulmonary disease and asthma, as well as cardio-myopathy disease. Relevant models enable experiments under physiologic conditions and are key for developing new therapies for chronic diseases.

"PromoCell now offers a large selection of donor cells with known disease status that are suitable for drug discovery and research applications,” says Daniel Spatz, chief business officer of PromoCell. These disease cell types can be cultured using PromoCell’s matching growth media to ensure optimal cell growth performance.

The Olympus Provi CM20 monitoring system.

Among other advantages, with a digital record of cell growth and health, users can store, reuse and transfer their data, compare it with past results or compare it with data captured under different conditions. In a project that multiple people are working on when training new people, the CM20 system makes it simple for managers to check the team’s culture status.

With proven experience in regenerative medicine and expertise in optics, image analysis and data management, Olympus says it uniquely positioned to help empower users to push the boundaries of regenerative medicine with such technology. 

BioTek Announces the New Cytation 7

WINOOSKI, Vt.—The New Cytation 7 Cell Imaging Multi-Mode Reader from BioTek Instruments combines an automated upright microscope, an inverted microscope and multimode plate reader in a single instrument. This combination of microscopes and multimode reading enables applications that would typically require multiple instruments, the company states.

The inverted microscope supports fluorescence, brightfield and color brightfield imaging. The magnification range from 10x to 60x allows researchers to capture and analyze large objects as well as intracellular details with more ease. An upright reflected light microscope offers up to 8X magnification for applications such as ELLSpot, slide scanning with ROI detection and colony counting.

The multimode module in Cytation 7 features quadruple monochromator-based fluorescence, absorbance and luminescence. Temperature and gas control, plus variable shaking, provide an ideal environment for live cell assays. Gen5 Software controls the instrument for precise, accurate image and data capture as well as powerful data processing for quantitative and qualitative analysis.

Cytation 7 may be integrated with BioTek’s Brio Single-Well Nanoliter Robot, giving full imaging or multimode workflow automation for up to eight microliter wells at once.

Faster time to clinical candidate using FEP activity prediction

CAMBRIDGE, U.K.—Cresset, a provider of software for molecule discovery and design, recently released fully validated and accessible free energy perturbation (FEP) calculations and new workflows in Flare V5, one of the leading solutions for structure-based design.

According to the company, it is now common seen as best practice in lead optimization projects to use methods such as FEP to calculate binding energies and, therefore, predict compound activities ahead of committing to time-consuming and expensive synthesis and wet lab screening. Adoption of these methods saves time, cost and resources, and enables better decision-making in late-stage preclinical discovery.

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Antabio’s PEI might significantly enhance current CF therapy

JUPITER, Fla.—Researchers at the Florida campus of The Scripps Research Institute have developed a drug-like compound that selectively prevents production of an underlying cause of Parkinson’s disease, a disordered protein called alpha-synuclein. The study reportedly underscores the untapped potential of addressing diseases mediated by “undraggable” proteins via the messenger RNAs that encode them.

The results were part of a study paper titled “Translation of the intrinsically disordered protein alpha-synuclein is inhibited by a small molecule targeting its structural mRNA,” published in the Proceedings of the National Academies of Sciences the week of Dec. 30. The study was authored by Scripps Research chemistry professor Dr. Matthew D. Disney, graduate student Peiyuan Zhang and colleagues.

For a gene to actually encode a protein, it must first be translated with the help of messenger RNA. The messenger RNA serves as a template for protein production, a process called translation, which is orchestrated by molecular machines called ribosomes.

Disney’s alpha-synuclein compound, which he named Synucleozid, stops the ribosome from detecting the messenger RNA template, thus preventing the translation or “printing” of the problematic alpha-synuclein protein. The Scripps team collaborated on the study with a team from Rutgers University led by Dr. M. Maral Mouradian, director of the Institute for Neurological Therapeutics.

“We showed not only that we can inhibit the translation of alpha-synuclein, which is an important protein in Parkinson’s disease and dementia, but also we showed that this compound can stop its messenger RNA from being recognized by a ribosome,” Disney said. “In other words, the compound doesn’t allow the messenger RNA to be made into the alpha-synuclein protein. We believe this unique mechanism is broadly applicable.”

Disney has spent more than a decade building technologies capable of identifying drug-like compounds to do this. A system he invented called Informa computationally uses genetic sequence to predict complementary small molecule-RNA interactions.

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

Antabio’s PEI might significantly enhance current CF therapy

LAEßE, France—Antabio SAS, a biopharmaceutical company focused on developing a broad pipeline of antibacterial treatments against life-threatening World Health Organization critical priority pathogens, announced in early January that it had been awarded up to $4.4 million in a second tranche funding from CARB-X, a global non-profit partnership dedicated to tackling the global rising threat of drug-resistant bacteria. The funding is to support the development of Antabio’s small molecule candidate for the treatment of Pseudomonas aeruginosa infections in cystic fibrosis (CF) patients.

This new tranche, part of a CARB-X award announced in July 2017, will be used to advance Antabio’s Pseudomonas Elastase Inhibitor (PEI) program up to completion of non-GMP preclinical studies. The additional funding recognizes Antabio’s success in advancing a profound milestone during the first contractual period leading to the identification of a preclinical candidate.

Antabio’s PEI program seeks to develop an inhalable product to be used as an adjunct to existing therapy, one which will aim to reverse the severity of P. aeruginosa disease and enhance pathogen clearance by targeting the LasB elastase, a key virulence determinant that contributes to tissue damage and inflammation in infected CF lungs. Antabio believes the PEI product, with its novel target and groundbreaking mechanism of action, has the potential to significantly enhance the effectiveness of existing treatments for CF patients.

MorphoSys submits BLA for tafasitamab

PLÄNNE, Germany—MorphoSys AG announced recently that it has submitted a Biologics License Application (BLA) to the U.S. Food and Drug Administration for tafasitamab, an anti-CD19 antibody, for the treatment of relapsed or refractory diffuse large B cell lymphoma (r/r DLBCL). The BLA submission is based on the primary analysis data from the L-MIND trial of tafasitamab in combination with lenalidomide in patients with r/r DLBCL and the retrospective observational matched control cohort Re-MIND evaluating efficacy outcomes of r/r DLBCL patients who received lenalidomide monotherapy.

“The BLA submission marks a significant milestone in MorphoSys’ history and demonstrates our dedication to address the high medical need in relapsed or refractory DLBCL.” Dr. Malte Peters, chief development officer of MorphoSys.

Tafasitamab (designated as MOR208 in MorphoSys’ investigational pipeline) is a humanized Fc-engineered monoclonal antibody directed against CD19. Fc-modification of tafasitamab is intended to lead to a significant potentiation of antibody-dependent cell-mediated cytotoxicity and antibody-dependent cellular phagocytosis, thus aiming to improve a key mechanism of apoptosis. Tafasitamab has been observed in preclinical models to induce direct apoptosis by binding to CD19, which is assumed to be involved in B cell receptor signaling.

“New tech allows control of gene therapy doses

JUPITER, Fla.—Scientists at Scripps Research have developed special switch-like molecules that can be embedded in gene therapies to allow for controlled dosing of those therapies over wide ranges in individual patients.

The feat, reported in Nature Biotechnology, offers gene therapy designers what may be the first viable technique for adjusting the activity levels of therapeutic genes in patients. The lack of such a basic safety feature has limited the development of gene therapies, which have otherwise held great promise.

The scientists demonstrated the power of their new switching technique by incorporating it into a gene therapy that produces the hormone erythropoietin (EPO), used as a treatment for anemia. They showed that they could suppress the expression of the EPO gene to very low levels with a special embedded molecule, and could then increase the gene’s expression, over a wide dynamic range, using injected control molecules called morpholinos that the U.S. Food and Drug Administration has found to be safe for other applications.

“We think that our approach offers the only practical way at present to regulate the dose of a gene therapy in an animal or a human,” said principal investigator Dr. Michael Farzan, co-chair of the Department of Immunology and Microbiology at Scripps Research.

Most drugs on the market work by binding to problematic proteins to limit their ability to cause harm. However, for a drug to bind, those proteins must have stable structures with favorable binding pockets. The alpha-synuclein protein is one example of many in the genome that have confounded scientists’ efforts to bind with medications, due to their undefined structure.

Disney noted that the so-called “druggable genome” is currently comprised of only about 3,000 genes out of an estimated 20,000 protein-coding genes. Disney’s research suggests that many undraggable proteins are transcribed by RNA that do have stable structures, meaning the RNA should be druggable, offering a potentially effective workaround.

INTEGRA Biosciences AG

Get more information at www.integra-biosciences.com
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