An ‘intelligent’ approach

AI and machine-learning approaches seem to be an industry theme for Q1 2018

BY KELSEY KAUSTINEN

MCLEAN, Va.—It might not have been the Super Bowl, but another “bowl” competition was announced in the first quarter of the year: the fourth annual Data Science Bowl, launched by Booz Allen Hamilton and Kaggle and hosted in partnership with the Broad Institute of MIT and Harvard, NVIDIA and PerkinElmer. The Data Science Bowl is a 90-day competition in which participants are challenged to train deep learning models to assess images of cells and identify nuclei, without human intervention and regardless of experimental setup. Those who create the best algorithms will split $170,000 in cash and prizes, including an NVIDIA DGX Station, a personal artificial intelligence (AI) supercomputer that provides a computing capacity of 400 CPUs in a desktop workstation.

“This year’s Data Science Bowl will bring together thousands of people from around the world to confront deadly diseases in one of our most complex challenges yet,” said Ray Hensberger, a Booz Allen Hamilton principal. “Despite some progress, it remains time-consuming and expensive to find treatments for all types of diseases. We believe that pairing artificial intelligence and the collective ingenuity of the global data science community will yield powerful tools that can help accelerate the search for medical cures.”

The Broad Institute will provide participants “with data from thousands of nuclei from a wide variety of imaging experiments,” Zlotnick added, “there is a great vacuum in any cell image. Per the release, this competition could help fill a needed void in AI-based early-stage research: “All current options for nuclei detection require time-consuming biologist intervention. There are options for nuclei detection require time-consuming biologist intervention. There are

‘Virus-cracking’ molecules

Indiana University team fights hepatitis B

BY ILENE SCHNEIDER

BLOOMINGTON, Ind.—Globally, about two billion people have had a hepatitis B virus (HBV) infection in their lifetime, and more than 240 million live with chronic infection. While a vaccine exists, there is no cure.

Adam Zlotnick, a professor in the Indiana University Bloomington College of Arts and Sciences’ Department of Molecular and Cellular Biochemistry, whose research team has made an important step forward in the design of drugs that fight the hepatitis B virus, explained, “HBV is a deadly disease. More than 700,000 people die each year from HBV. Chronic HBV patients are at much greater risk of liver cancer, cirrhosis and liver failure. They are also at risk of passing the virus on to others.” Zlotnick added, “There is a great vaccine for HBV. Every infant should be vaccinated. There are medicines available that will suppress the virus. These ‘nucleoside analogs’ block the viral

HBV CONTINUED ON PAGE 18

TAG TEAM AGAINST USHER SYNDROME

Foundation Fighting Blindness and ProQR enter into a partnership to develop QR-421a for genetic disease

BY MEL J. YEATES

COLUMBIA, Md. & LEIDEN, The Netherlands—Foundation Fighting Blindness and ProQR Therapeutics N.V. recently announced a partnership to develop QR-421a for Usher syndrome 2A. Under the agreement, Foundation Fighting Blindness will provide up to $7.5 million in funding to ProQR for the preclinical and clinical development of QR-421a. Usher syndrome is a devastating genetic disease in which patients first develop hearing loss and then progressive vision loss. Currently there is no treatment for the ophthalmic manifestation of Usher syndrome type 2A.

According to Smital Shah, chief financial officer of ProQR, “QR-421a is a first-in-class investigational RNA-based oligonucleotide designed to address the underlying cause of Usher syndrome 2A due to mutations in exon 13 of the USH1C gene. Mutations in this exon can cause loss of functional usherin protein. As a result of the loss of this protein, patients lose their hearing and then sight by mid-adulthood, leading to numerous educational, workplace and life challenges. QR-421a is designed to repair the genetic defect

ProQR Therapeutics N.V. (pictured here) recently partnered with Foundation Fighting Blindness to develop QR-421a as a treatment for Usher syndrome 2A.

ProQR Therapeutics N.V. (pictured here) recently partnered with Foundation Fighting Blindness to develop QR-421a as a treatment for Usher syndrome 2A.

CONTINUED ON PAGE 32
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STRONG OUT OF THE STARTING GATE
This year is already posting big numbers for merger and acquisition activity

BY JEFFREY BOULEY

JUST A MONTH OR SO into this year, notes data and analytics company GlobalData, biotech merger and acquisition (M&A) deal activity has already skyrocketed. As the firm said in a recent news release, “Acquisitions from colossal drug makers Celgene and Sanofi total more than $26 billion combined, and the companies have indicated a focus to expand their oncology and hematology portfolios. Many other large pharma firms are expected to join the race and boost their product portfolios through M&As.”

Just to recap a few of the big early deals in 2018 already—and just in January alone, no less:
- Sanofi announced plans to acquire Ablynx for $4.8 billion and hemophilia-focused Bioverativ for $11.6 billion
- Celgene bought up chimeric antigen receptor T cell (CAR-T)-specialist Juno Therapeutics for approximately $9 billion—mere weeks after acquiring Impact Bio-medicines for as much as $7 billion.

As GlobalData notes, the question now turns to what implications these deals might have for both pharmaceutical companies and for other players in the biotech industry, “and whether or not the streak is likely to continue.”

Ashwin Oberoi, a healthcare analyst at GlobalData, commented that “Although Celgene expects Juno’s CAR-T drug lisocabtagene maraleucel to gain approval in 2019, this therapy is a late market entrant behind Novartis’ Kymriah...”

IPO CONTINUED ON PAGE 4

Checking on the IPOs

WE ARE NO STRANGERS to covering collaboration deals, mergers and acquisitions or news of startups and spinouts. What we cover a bit less are the initial public offerings (IPOs) when companies decide to go public. So, to remedy that, we bring you this month a roundup of three recent IPOs.

SOL-GEL PUTS SKIN IN THE GAME

NESS ZIONA, Israel—Sol-Gel Technologies Ltd., clinical-stage dermatology company focused on identifying, developing and commercializing branded and generic topical drug products for the treatment of skin diseases, announced Feb. 5 the closing of its initial public offering (IPO) of 7,187,500 ordinary shares at a public offering price of $12 per ordinary share. The aggregate gross proceeds to Sol-Gel from the offering were approximately $86.3 million, before deducting underwriting discounts and commissions and estimated offering expenses. The ordinary shares commenced trading on The Nasdaq Global Market on Feb. 1 under the ticker symbol SGL.

Jefferies LLC and BMO Capital Markets Corp. acted as joint book-running managers for the offering. JMP Securities LLC and Raymond James & Associates Inc. acted as co-managers.

Sol-Gel’s current product candidate pipeline consists of late-stage branded product candidates that leverage its proprietary silica-based microencapsulation technology platform, as well as several generic product candidates across multiple indications.

A ‘SOLID’ START FOR GOING PUBLIC?

CAMBRIDGE, Mass.—Late January saw Solid Biosciences Inc. announce today the closing of its IPO of 8,984,375 shares of its common stock, sold by the company at a public offering price of $16 per share. This includes the exercise in full by the underwriters of their overallotment option to purchase an additional 1,197,925 shares.

Solid Biosciences is a clinical-stage company focused on developing gene therapy for certain severe, life-threatening rare diseases. Solid Biosciences was founded in 2014 and is headquartered in Cambridge, Massachusetts.

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MARKET NEWS

M&A CONTINUED FROM PAGE 3

and Gilead’s Yescarta, both of which are CAR-T therapies that were approved in 2017. Celgene is taking a huge risk by assuming that lisocabtagene maraleucel can successfully steal market share from the other two CAR-T therapies.”

Fundamentally, large drug developers are facing pressure from maturing markets and require opportunistic deals to spur revenue growth. GlobalData believes that Merck, Pfizer and Amgen are all plausible candidates to expand via M&A. All these large pharma companies have huge offshore cash stores and are likely to make an acquisition to boost their mid-/late-stage pipeline.

“Companies that remain as likely targets generally include those with therapies that have recently gained approval or are likely to gain approval within high-impact disease areas,” said Oberoi. “Generally, interest is strong in companies that focus on oncology, rare diseases and gene-editing technologies, such as BioMarin, Clovis Oncology, Puma Biotech and Bluebird Bio.

“There is also high interest in companies that focus on aging-related diseases, had closed its IPO of 6,516,667 shares of common stock at a public offering price of $15 per share, which included the exercise in full by the underwriters of their option to purchase up to 850,000 additional shares. The gross proceeds from the offering are expected to be $97.8 million, before deducting underwriting discounts and commissions and estimated offering expenses. The shares commenced trading on the NASDAQ Global Select Market on Jan. 26 under the ticker symbol TORC.

BoA Merrill Lynch, Leerink Partners and Evercore ISI acted as joint book-running managers for the offering. Wedbush PacGrow acted as a co-manager for the offering. A new future in store for Restorbio

Boston—Late January brought news that resTORbio Inc., a clinical-stage biopharmaceutical company focused on the development and commercialization of novel therapeutics for the treatment of aging-related diseases, had closed its IPO of 6,516,667 shares of common stock at a public offering price of $15 per share, which included the exercise in full by the underwriters of their option to purchase up to 850,000 additional shares.

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A biopharmaceutical company focused on the development and commercialization of novel therapeutics for the treatment of aging-related diseases, resTORbio’s lead program focuses on selective inhibition of the target of rapamycin complex 1 (TORC1) pathway to treat aging-related diseases with an initial focus on diseases caused by immunosenescence, the decline in immune function that occurs during aging.

IPO CONTINUED FROM PAGE 3

their overallotment option to purchase up to 1,171,875 additional shares of common stock from the company—trading under the ticker symbol SLDB—at the same price. Including the proceeds from the sale of these additional shares, Solid Biosciences received total net proceeds of approximately $133.7 million from the offering, after deducting the underwriting discounts and commissions, but before deducting estimated offering expenses.

J.P. Morgan, Goldman Sachs & Co. LLC and Leerink Partners acted as joint book-running managers of the offering, and Nomura and Chardan acted as co-managers for the offering.

Solid Biosciences is a life-science company focused solely on finding meaningful therapies for Duchenne muscular dystrophy (DMD). Founded by those touched by the disease, Solid aims to be a center of excellence for DMD, bringing together experts in science, technology and healthcare to drive forward a portfolio of candidates that have life-changing potential. Currently, Solid is progressing programs across four scientific platforms: corrective therapies, disease-modifying therapies, disease understanding and assistive devices. The company’s lead candidate, SGT-001, is an adeno-associated viral vector-mediated gene therapy, which is currently under investigation in a Phase 1/2 clinical trial called IGNITE DMD.

Ashwin Oberoi, a healthcare analyst at GlobalData in January 2018, this trend is expected to continue throughout the year. As a result of the major surge in growth of the biotech industry through improved earnings, economic growth and recent deal activity, the sector is poised to reach an all-time record high.

And speaking of both Merck and GlobalData, and thoughts by the latter about the former, it looks like Merck might lead pharma to the top of the GlobalData list in 2018. As GlobalData points out, the pharmaceutical industry is “highly volatile, with promising lead candidates making or breaking a company’s year.” Companies’ financial success is often down to which strategic deals they are able to make with other pharmaceutical companies and research organizations to enable them to develop the next leading drug in the market.”

The $8.8 billion agreement between AstraZeneca and Merck to co-develop AstraZeneca’s Lynparza (olaparib) for multiple cancer types reached $2.65 billion across 1,490 transactions with a drop in the number of megadeals (those over $10 billion), leaving the sector at its lowest value for four years.

The PMB sector accounted for an 8.4-percent market share of global M&A vs. the 8.7-percent mark of the previous year; however, interest in the sector by investors and corporates remains steady, following the third successive year in which the sector recorded a market share by deal count of over 8 percent.

While the year saw scientific milestones reached—such as the CAR T therapies by Novartis, or more recently, the first FDA-approved gene therapy of Spark Therapeutics—the PMB sector continued to experience significant technological and scientific changes—deals in 2017 reached $2.65 billion across 1,490 transactions with a drop in the number of megadeals (those over $10 billion), leaving the sector at its lowest value for four years.

M&A CONTINUED FROM PAGE 3

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Ashwin Oberoi, a healthcare analyst at GlobalData, added: “Despite this, Merck has had an arguably more successful year. It more than quadrupled its alliance deal values since 2016, and if its subsidiaries are added to the equation, its 2017 deal values rise to $9.5 billion, an increase of 248 percent from 2016, where AstraZeneca and its subsidiaries stayed almost stagnant at $1 billion.”

Pieir Pharmaceuticals also saw a good year, making alliances in 2017 worth more than 35 times those it made in 2016, though GlobalData expects it will do less well in 2018. Allergan and Novartis both experienced slower years than 2016, with decreases in partnership and licensing deal value by 44 percent and 5 percent, respectively. However, both companies still closed big deals in 2017. In the end, though, GlobalData expects that 2018 “is likely to be Merck’s year in terms of research and development collaboration.”

And with all this talk about early 2018 M&A activity, how about a last look at 2017? According to Mergermarket, an Acuris company—specifically according to its global M&A roundup report for the pharma, medical and biotech (PMB) sector for the year of 2017—here are some key takeaway points:

• PMB M&As fell short of sky-high figures achieved in recent years as the sector continued to experience significant technological and scientific changes—deals in 2017 reached $2.65 billion across 1,490 transactions with a drop in the number of megadeals (those over $10 billion), leaving the sector at its lowest value for four years.

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• While the year saw scientific milestones reached—such as the CAR T therapies by Novartis, or more recently, the first FDA-approved gene therapy of Spark Therapeutics—the PMB sector continued to come under heavy pricing pressures and political challenges. In the end, the top 10 M&A deals accounted for 41.6 percent of the sector’s entire combined value at $10.2 billion, and Johnson & Johnson’s $25.6-billion bid for Actelion Pharmaceuticals topped them all.

MARKET INDICES

Pharmaceutical Index

Biotechnology Index

IPO CONTINUED FROM PAGE 3

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CONTINUED FROM PAGE 3

MARKET NEWS

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BRIEFS

BMS files IND, extends work with Five Prime

SOUTH SAN FRANCISCO, Calif.— A milestone has been reached by Five Prime Therapeutics Inc. in its agreement with Bristol-Myers Squibb. The latter company submitted an IND application to the FDA for a therapeutic candidate developed under the immune checkpoint pathway discovery collaboration between Five Prime and BMS, triggering a $5-million milestone payment to Five Prime.

The candidate in question is a fully human monoclonal antibody targeting TIM-3 (T cell immunoglobulin and mucin domain-3), an immune checkpoint receptor. Alongside this milestone, BMS has exercised its option to extend its collaboration with Five Prime, which will now last until March 2019, providing Five Prime with further funding for the expanded research term. The agreement grants BMS exclusive worldwide rights to develop and commercialize products against select protein targets in three checkpoint pathways.

Heptares reports structure of complement C5a receptor

TOKYO & LONDON—In January, Heptares Therapeutics published work alongside the first high-resolution X-ray crystal structure of the complement C5a receptor binding a small-molecule allosteric antagonist. These results have detailed the location of a new allosteric binding site for the GPCR outside of the transmembrane helical bundle. The C5a receptor features in the innate immune response and is part of the complement system, which partly comprises the body’s response to infection and injury.

Fiona Marshall, chief scientific officer of Heptares and Sosei, said: “Our ability to determine the structures of GPCRs with high definition alongside access to more than 640 million pharmaceutical-oriented molecules, making it the largest accessible compounds to date. Enamine is able to assemble new compounds through single-step combinations of the 150,000 building blocks it has available. By using the most characterized (readily accessible) virtual compound concept. This new tool offers easy search-and-find access to more than 640 million pharmaceutical-oriented molecules, making it the largest chemical space of commercially accessible compounds to date. Enamine can ensure a minimum synthesis rate of 80 percent and a delivery time of just three to four weeks. To complement this, BioSolveIT’s software offerings enable users to easily and effectively search a massive chemical library that would be daunting with standard

Getting the ‘Akt’ straight in angiogenesis

Sanford Burnham Prebys Medical Discovery Institute (SBP) as being pivotal for angiogenesis could offer a better option. This work was detailed in a paper titled “R-Ras-Akt axis induces endothelial lumenogenesis and regulates the patency of regenerating vasculature,” which appeared in Nature Communications. VEGF does encourage vascularization, but as the team—led

Open-access communities launch to support drug discovery efforts

BY KELSEY KAUSTINEN

KIEV, Ukraine & SANKT AUGUSTIN, Germany—Crowdsourcing is far from a new tactic, being as it is a cheaper and sometimes faster option of advancing new ideas, especially for individuals or smaller organizations. But this approach is being harnessed by a handful of larger pharmaceutical firms as well, in separate efforts aimed at spurring the identification of promising new molecules and finding therapeutics for a neglected disease.

Chemical research organization Enamine Ltd., which boasts the world’s largest collections of building blocks and screening compound libraries, and BioSolveIT GmbH have launched the REAL Space Navigator, a jointly developed software tool that leverages Enamine’s REAL (readily accessible) virtual compound concept. This new tool offers easy search-and-find access to more than 640 million pharmaceutical-oriented molecules, making it the largest chemical space of commercially accessible compounds to date. Enamine can ensure a minimum synthesis rate of 80 percent and a delivery time of just three to four weeks. To complement this, BioSolveIT’s software offerings enable users to easily and effectively search a massive chemical library that would be daunting with standard

In recent months, some significant players in the pharma R&D realm have tapped into the crowdsourcing concept to aid in discovery efforts.

COMPUGEN CATCHES A NEW CHECKPOINT

Discovery of ILDR2 as a novel immune checkpoint and potential for autoimmune diseases published in back-to-back papers

BY MEL J. YEATES

TEL AVIV, Israel—Compugen Ltd. announced in early February the publication of the discovery and validation of the ILDR2 protein as a novel immune checkpoint, and its use as an Fc fusion protein for the treatment of autoimmune diseases, in two peer-reviewed papers in The Journal of Immunology. According to Dr. Zurit Levine, vice president of research and discovery at Compugen, “ILDR2 (CGEN-15001T) is a member of the immunoglobulin superfamily (IgSF), which was identified by Compugen’s computational discovery platform as a novel By-like protein based on shared bioinformatic characteristics with known B7 members. Proteins of the B7 family play a pivotal role in regulating immune responses and have thus became attractive targets for development of novel drugs for cancer immunotherapy and autoimmune diseases.”

“Our prediction that ILDR2 is a novel immune checkpoint was supported by its inhibition of T cell activation both when expressed as a natural membrane protein and as an Fc-fused protein composed of the extracellular domain of ILDR2 fused with IgG Fc.”

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search tools. REAL Space Navigator can be used on standard computers without even the need for connect-
ing to the internet.

Michael Bosseert, head of strategic alliances at Enamine, commented: “The drug discovery industry has an enormous interest in new chemical compounds. Our REAL concept provides an efficient solution for virtual screening initiatives and analog searches to our clients, who appreciate going beyond the availability bias. BioSolveIT’s fantastic team and its exceptional software platforms have already expanded the borders of Enamine’s REAL database. We will continue to evolve this and hope to put billions of our future tangible molecules at researchers’ fingertips.”

Neither BioSolveIT nor Enamine plan to let this new community resource rest on its laurels, either—they intend to continue collaborating, with a goal of expanding the database to more than one billion compounds by the end of the second quarter of 2018.

Around the same time, another partnership—this one consisting of the University of Sydney, Erasmus MC and the Drugs for Neglected Diseases initiative (DNDi)—announced the launch of the Myceto Open Source (MycetOS) project. This initiative will apply an open pharma approach to the discovery of compounds that could result in new treatments for patients with fungal mycetoma (eumycetoma), a tropical infectious disease that attacks skin, deep muscle and bone, resulting in deformities that frequently lead to amputation and permanent disability. There are existing treatment options, but they are often toxic, ineffective and expensive.

The point of MycetOS is to advance drug discovery efforts by offering a fully transparent online presence and soliciting community-driven, in-kind scientific contributions. All ideas and results will be shared real-time in an open-access database, with Twitter and a subreddit in use for community discussion. The first step will consist of making a manuscript, “Analogues of fenarimols as novel drug candidates for mycetoma,” available for the global scientific community to review. The manuscript was submitted with its full dataset to bioRxiv, an open-access biology preprint server, for community review and comments, and details the results of efforts to screen 800 diverse, drug-like molecules for active compounds against the causative pathogen of eumycetoma. MycetOS participants from the University of Sydney, Erasmus MC and DNDi co-authored the manuscript, as did partners at the Medicines for Malaria Venture, which also provided the molecules for screening from their Stasis and open-access Pathogen Boxes.

“We invite anyone interested to review not only the manuscript but also the dataset, and to join this Open Pharma drug discovery project for mycetoma,” commented Dr. Mat Todd, associate professor at the University of Sydney. “Forward movement of the work looks to the participation of interested researchers and others. This is already happening successfully with a previous Open Pharma project, Open Source Malaria (@OS_M).”

“While MycetOS was developed by participants from the University of Sydney, Erasmus MC and DNDi, it is not ‘owned’ by any of us,” said Wendy van de Sande, associate professor at Erasmus MC. “This early work merely starts a process of discovering potential new chemical entities for eumycetoma, and we invite anyone interested to identify how they might contribute and participate as an equal partner in this search for a new treatment for this most neglected of tropical diseases.”

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Researchers at the Sanford Burnham Prebys Medical Discovery Institute recently detailed how the protein kinase Akt and the protein R-Ras are critical to supporting new blood vessel growth.

SBP CONTINUED FROM PAGE 6

by Dr. Masanobu Komatsu, associate professor at SBP’s Lake Nona campus—showed with 3D culture and living tissue, the resulting vessels are unstable and non-functional. Specifically, “Functional vessels need to have a lumen, a pipe-like opening that allows oxygenated blood and nutrients to travel through the body, and VEGF alone cannot fully support the formation of such a vessel structure,” Komatsu said in a press release. As the authors note in their paper, “The formation of endothelial lumen is fundamental to angiogenesis and essential to the oxygenation of hypoxic tissues.”

The other needed parts of the process are Akt, a protein kinase, and the protein R-Ras. Akt is activated by R-Ras, a Ras homolog, which then “stabilizes the microtubule cytoskeleton in endothelial cells leading to endothelial lumogenensis,” per the paper. In contrast, “The activation of Akt by the potent angiogenic factor VEGF-A does not strongly stabilize microtubules or sufficiently promote lumen formation, hence demonstrating that isolated Akt does not generate functional blood vessels,” Dr. Masanobu Komatsu, a press release.

The team began their work in vitro with a fibrin gel 3D culture of endothelial cells. Endothelial cells were coated onto microbeads and embedded in fibrin gel with pericytes seeded on the top of the gel as feeder cells, the authors wrote. Silencing R-Ras with short hairpin RNA proved to disrupt lumogenesis in the endothelial cells, and many of the cells did not undergo morphogenesis.

“Generating new blood vessels is similar to the way trees grow, sprouts develop from existing vessels and then branch out further and further to restore vascularity,” said lead author Dr. Fangxue Li, a postdoctoral associate in Komatsu’s lab. “We hypothesized that R-Ras-dependent mechanisms contribute to the structure of new blood vessels.”

The team moved to rodent’s, their in vivo work in mice demonstrated that R-Ras activating Akt is a pivotal part of the process of lumogenensis in “replicative angiogenesis.” Without R-Ras, the authors note, an abundance of vessels develop in ischemic tissue that lack lumens, which means they are useless for circulation and do not aid recovery.

Komatsu said “In our study, we found that if you upregulate R-Ras expression, the lumen-forming vessels become more stable and mature. This is because you can repair the function of blood vessels by upregulating R-Ras, and R-Ras uses the Akt pathway for promoting vessel maturation.”

“We propose that VEGF and R-Ras activation of Akt signaling are complementary to each other—both are necessary to generate fully functional blood vessels to repair ischemic tissue,” Komatsu explained. “Our next step is to work toward promoting the combined signaling of Akt in clinical studies, prompting R-Ras activation through either gene therapy or pharmacologically in parallel with VEGF therapy.”

The difficulty lies in the fact that R-Ras is difficult to target therapeutically, he notes. “Akt is one of the downstream R-Ras signaling pathways that we looked at,” Komatsu says. “We also have found several other downstream pathway mechanisms, but what we still don’t know much about is the upstream of R-Ras. We don’t know how R-Ras expression is regulated by blood vessels. The new question is, how can you upregulate R-Ras? Now we are looking into the upstream mechanisms, regulators of the R-Ras gene. And once we find those regulators, hopefully some of those regulator pathways are easy to target. R-Ras is not an ideal target, but maybe the upstream of R-Ras can provide a new target that can be druggable.”

This work was funded in part by the National Cancer Institute, the National Science Foundation Grant, the American Heart Association, the Bankhead-Coley Cancer Research Program and the Florida Breast Cancer Foundation.

UC San Diego researchers recently described new technologies that enable a detailed analysis of how genetic mutations and chemical compounds affect the molecular machinery inside a cell, which could help identify new targets for drug discovery and therapy. The two papers are titled “Systematic Gene-to-Phenotype Arrays: A High-potential analysis—machine learning—is needed to make sense of all the data. This to end, Jaeger founded BiocipherX Inc., a startup company that is currently developing this new drug discovery and prediction approach.

A better heart model? SAN DIEGO—In early 2018, in what is being touted as first-of-its-kind preclinical ex vivo human cardiac research, Anal Bios and Angen published work in the journal Frontiers in Physiology demonstrating the translational heart failure model, combined with integrated analysis using a newly developed pro-arrhythmic score, can
“Data from this research demonstrates that isolated adult human ventricular tissue enables the generation of reliable and predictive data for human-focused cardiac safety assessment at early stages in drug discovery, provides a good opportunity to prioritize compounds and eliminates the potential for cross-species differences.”

Dr. Najah Abi-Gerges, vice president of R&D for AnaBio

The importance of native kinase profiling

LA JOLLA, Calif.— ActivX Biosciences Inc., a wholly owned subsidiary of Tokyo-based Kyorin Pharmaceutical Co. Ltd., announced in mid-January two reports published in peer-reviewed journals by Prof. Nathaniel Gray at the Dana Farber Cancer Institute, Jay Bradner of Novartis and their colleagues, in which the KiNativ platform was used to generate critical data supporting these studies.

Selective protein kinase degrader using heterobifunctional molecules consisting of separate binding elements for a kinase active site and an E3 ubiquitin ligase has emerged as a promising new modality for drug development, according to ActivX. In contrast to the traditional approach of inhibiting the enzymatic activity of a kinase, once these bifunctional compounds bind to the targeted kinase, they recruit the ubiquitin-ligase which then can lead to quantitative loss of target enzyme through proteasome-dependent degradation. Several companies have been founded to develop such compounds, including Arvinas, C4 Therapeutics and Kymera.

In both publications, well-characterized kinase inhibitors were converted to degraders by conjugation with a thalidomide derivative that binds the Cereblon E3 ubiquitin ligase. In one report, published in Cell Chemical Biology, a promiscuous kinase inhibitor was converted to a degrader. Quantitative proteomics was used to identify 28 out of about 300 kinases that underwent degradation. The initial results were then used to guide the development of selective degraders for FLT3 and BTK.

In the second report, published in Nature Chemical Biology, a CDK binding element was converted into a degrader, yielding a CDK9 selective degrader.

In both studies, the KiNativ platform was used to monitor the kinases that bound the degraders by measuring in-cell target engagement. Importantly, the number of kinases that bound the degraders was significantly higher than the number of kinases that underwent degradation, indicating that there is not a straightforward correlation between the affinity of a degrader for a kinase and its ability to degrade the kinase.

Thus, the KiNativ platform reportedly provides a unique approach to monitoring the kinases capable of binding a degrader by interrogating those kinases that are in fact degraded, compared to those that inhibit the targeted kinase but are not slated for degradation.

“2018 will be the year we see an exponential increase in the number of small-molecule degraders targeting a host of different protein targets,” Gray predicted. “As the efficiency of degradation does not exclusively depend on typical parameters around target occupancy, proteomic technologies (both gene-family directed and global) that quantitatively measure protein abundance will be critical to evaluating the selectivity of new degrader molecules.”

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The new Vi-CELL BLU Cell Viability Analyzer from Beckman Coulter.

Before we upgraded our Vi-CELL XR, we asked labs around the world what improvements they wanted to see. As a result, our new Vi-CELL BLU is a next-generation cell viability analyzer with faster processing speeds, expanded sample capacity (choose between a 24-position carousel and a 96-well plate loader), minimized sample test volumes (as low as 200 μL), improved instrument-to-instrument comparability, and a smaller footprint (just 16.5” x 21.2”).

Learn more about Vi-CELL BLU now, at info.beckmancoulter.com/ViCELLBLU
At Nuritas our mission is to positively impact billions of lives worldwide, and we therefore are delighted to be collaborating with Nestlé, the world’s largest food and beverage company on such an important project. We are really looking forward to beginning this impactful journey together,” said Nora Khaldi, founder and chief scientific officer of Nuritas.

“As our understanding of food and nutrition continues to grow, our global research and development network is looking ahead to discover how we can help enhance quality of life and contribute to a healthier future for everyone. Research partnerships such as that with Nuritas help us achieve that goal,” added Richard Stadler of the Nestlé Research Centre.

Other discovery and validation efforts are underway in the British Isles as well. Medical research charity LifeArc (previously MRC Technology) and the Milner Therapeutics Institute at the University of Cambridge have partnered to identify and validate drug targets in immuno-oncology and respiratory diseases. The Milner Therapeutics Institute is a fully integrated institute of the School of Biological Sciences and the School of Clinical Medicine at the University of Cambridge, and for its part, LifeArc has helped contribute to the development of drugs such as Keytruda, Actemra, Tyasabri and Entyvio.

“Drug discovery is a long and risky process, and our collaboration with the Milner Therapeutics Institute represents a powerful way to unlock new potential approaches to help patients,” Dr. Justin Bryans, executive director of drug discovery at LifeArc, said in a press release. “We are excited about the opportunity to work at the interface of drug discovery and AI and apply the knowledge in this field to help expedite the delivery of new treatments to patients.”

The partnership will unite the machine learning and bioinformatics of the Milner Therapeutics Institute with LifeArc’s expertise in drug discovery in hopes of not just discovering new targets, but developing new machine learning-based approaches to discovering novel therapeutic targets, stratifying patient populations and predicting drug efficacy. LifeArc’s capabilities include assay development, screening with a library of more than 120,000 compounds, hit-to-lead optimization, proof-of-concept work and ADME/DMPK.

Prof. Tony Kouzarides, director of the Milner Therapeutics Institute, commented:

“We are delighted to be working closely with LifeArc in applying artificial intelligence and machine learning approaches to drug discovery. There is a lot of interest in these methods for the potential benefit of patients. The drug discovery insight and investment from LifeArc will be important in realizing this.”

In other U.K. partnering news, Intellegens has launched a commercial collaboration with e-Therapeutics, the Oxford, U.K.-based pioneer of Network-Driven Drug Discovery. Under the collaboration, e-Therapeutics will apply Intellegens’ Alchemite AI platform to produce improved predictions, fix errors and fill gaps in the large-scale biological and chemical information repositories in e-Therapeutics’ proprietary databases.

“Alchemite is the first in a series of application-specific AI modules that we are developing at Intellegens,” said Dr. Gareth Conduit, chief technology officer and co-founder of Intellegens. “These will be designed to address specific, high-value data analysis bottlenecks that we are uncovering through our discussions with existing and potential customers. With these new modules, we intend to pursue new business opportunities in both the life sciences and other sectors.”

Conduit developed Alchemite after years of research, presenting a new method for analyzing sparsely populated matrices via deep neural networks and novel machine-learning approaches. This AI engine features Intellegens’ deep learning algorithm, which the company notes on its website is “capable of training models from data [which] can be as little as 0.05 percent complete. Trained models can be used to make new predictions, identify errors and maximize a set of desired parameters.”

Dr. Jonny Wray, head of discovery informatics at e-Therapeutics, noted that: “We already utilize machine learning heavily in our discovery platform to augment empirical biological and chemical data. Our partnership with Intellegens will enhance and extend our internal capabilities at the cutting edge of AI research and application.”
ILDR2

continued from page 8

(designated ILDR2-Fc or CGEN-15001),” says Levine. “As such, ‘switching off’ of this pathway by an antibody will unleash the regulation of T cells and enable an effective immune attack on cancer cells. On the other hand, ‘switching on’ the ILDR2 pathway, using ILDR2-Fc, downregulates immune response and is highly desired in conditions of uncontrolled immune response, such as in autoimmune diseases and transplantations.”

Antibody-based therapeutics targeting ILDR2, designated by Compugen as CGEN-15001T for immuno-oncology, were licensed to Bayer. Compugen retains the full rights to the fusion protein, designated as CGEN-15001, consisting of the extracellular domain of ILDR2 and an Fc domain, for potential use in autoimmune diseases.

The relevance for cancer immunothera-
p
dy is the flip side of CGEN-15001, meaning an antibody against the membrane protein ILDR2. Since we have shown that CGEN-15001T is a negative regulator of T cell activity, targeting this protein with an antibody therapeutic would overcome CGEN-15001T’s suppressive effect within the tumor microen-
vironment and result in a robust antitumor immune response,” Levine notes in regards to Bayer’s interest in ILDR2.

“[The unique mechanism of action of
CGEN-15001 combines immunomodula-
tion with restoration of immune homeosta-
sis and re-establishment of antigen-specific
immune tolerance, underlying its ability to
ameliorate autoimmunity. Both these traits
are highly desired for a broad range of auto-
immune diseases and are not well addressed with currently available therapies, which are
gen
tenly immunosuppressive or employ only one of these traits,” Levine continues.

“Tolerance induction represents a paradigm shift in the treatment landscape across mul-
tiple autoimmune diseases, addressing high unmet need, in either early intervention, treatment or remission in an established autoimmune disease—or even when thinking about drug-free remission.

“Unlike current therapies, ILDR2-Fc com-

bines immunomodulation and regulation of
immune homeostasis by downregulating pro-
inflammatory T cells while enhancing anti-
inflammatory and regulatory T cells. ILDR2-
Fc has been shown to re-establish Ag-specific
immune tolerance, leading to durable dis-
ease amelioration following a short period
of therapeutic intervention. The long-term
therapeutic effect of ILDR2-Fc appears to
be associated with its ability to enhance the
derifferentiation of regulatory T cells (Tregs).”

The publication led by Compugen’s sci-
entists describes the computational dis-
covery approach leading to the discovery of
ILDR2 as a novel immune checkpoint. The experimental validation of the role of
this protein as a negative regulator of T cell activity was established internally at
Compugen, as well in collaboration with scientists from three leading academic
institutions. The paper reports the benefi-
cial effects of CGEN-15001 in an animal
model of rheumatoid arthritis (RA), as well
as in a translational assay utilizing blood
cells from RA patients, which mimics the
deleterious interactions of immune cells in
the RA synovium. The latter study was led
by Prof. Iain B. McInnes, Mairhead Chair
of Medicine and director of the Institute
of Infection, Immunity and Inflammation
at the University of Glasgow.

“These findings assign a new role to the
ILDR2 protein, whose immune-related func-
tion was not previously known, and uncov-
er a novel pathway involved in immune
regulation. The expression pattern of this
protein, as well as its mechanism of action
elucidated in these two publications, involv-
ing the induction of immune tolerance and
restoration of immune homeostasis, offer a
potential novel treatment option for auto-
imune and chronic inflammatory condi-
tions,” McInnes said.

Preclinical research led by Compugen’s
scientists—along with Profs. Stephen Miller
and Joseph R. Podjoil from the Department
of Microbiology-Immunology and Interde-
partmental Immunobiology Center, Feinberg
School of Medicine, Northwestern Univer-
sity—was published in an additional paper
demonstrating the potential of ILDR2-Fc
fusion protein to address autoimmune and
inflammatory conditions, as well as the
mechanism of action underlying this activ-
ity. The data show the potent and long-lasting
immunomodulatory activity of ILDR2-Fc
fusion protein in animal models of mul-
tiple sclerosis (R-EAE) and type 1 diabetes, and its
ability to promote engraftment in an animal
model of bone marrow transplantation.

“CGEN-15001 was previously shown to
be effective in treating several autoimmune
diseases in animal models, including mod-
els of multiple sclerosis, rheumatoid arthri-
tis, type 1 diabetes and psoriasis. In some of
these models, a short period of treatment
with CGEN-15001 was shown to induce a
durable long-term response suggestive of
an immune tolerance mechanism. In addi-
tion, CGEN-15001 enhanced graft survival
in a model of bone marrow transplantation,
demonstrating induction of donor-specific
tolerance. The MOA of CGEN-15001, which
affords restoration of immune homeosta-
sis and re-establishment of immune tol-
erance, could be beneficial in a broad range of
autoimmune and inflammatory conditions,”
concludes Levine.  

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Editor’s focus: So much to share

BY JEFFREY BOULEY

If you are reading this editorial in the physical issue of the magazine (as opposed to online), I would like to apologize for any arm strain you might currently be experiencing. This is our most hefty installment of the magazine ever—our very first 64-page issue.

And, it’s not for nothing that we brought you a thick March offer- ing. This month features our annual pre-show coverage of one of the biggest and most important conferences for many of DDNews’ readers: the annual meeting of the American Association for Cancer Research (AACR). As AACR Annual Meeting Program Committee Chair Dr. Elaine Mardis put it at the scale of the event, “Given the breadth and types of cancer studies and cancer medicine these days, it is really difficult to achieve content that absolutely is in line with all of the recent research that’s happening.”

So, of course, attending AACR 2018—and if indeed you personally do—will fill your brain with a plethora of oncology information, but we can help pre-load your cranium, as he be your cranial onco- logy feature this issue as well. Immediately after the AACR 2018 show preview beginning on page 19 is our Spotlight on Oncology on page 25, which is not only a supplemental companion to the AACR pre-show coverage but also a kind of follow-up to our Special Focus on Cancer Research News last issue, which featured heavily on immuno-oncology. This Spotlight on Oncology takes a broader approach to rounding up recent cancer-related R&D news.

And did I say something about “filling your brain” and “pre-loading your cranium” earlier? Well, in that vein as well, we have yet another special feature this issue, our Special Focus on Neuroscience and Neurobiology. While it certainly stands alone as a roundup of recent research related to the brain and the rest of the central nervous system, it is also a kind of prelude and lead-in for our Special Report on Neuroscience by Randall C Willis that will appear in the April issue. That Special Report will focus on recent efforts to understand the microbiome’s potential to combat drug resistance in the Cannabis species, and in particular their impact on neurological conditions such as epilepsy, amyotrophic lateral sclerosis, Parkinson’s disease and autism spectrum disorder.

Technology and services get a kind of double-dose of coverage this issue, with not only our monthly “On the cutting edge” roundup on page 52, but also a two-page installment of our periodic Product, Services, and Software feature, which starts on page 50 and spotlights quite a lot of items related to exhibitors at AACR 2018.

And all of that in addition to the many non- oncology and non-neurotherapy therapeutic areas that are covered by news articles in this issue in our Discovery, R&D, Preclinical, Clinical Trials, Diagnostics, Contract Services and Business and Government Policy sections.

So, now that reading this has hopefully given those arms some rest, time to start turning those pages again. As always, thank you for being a reader and thank you for giving us a chance to provide this plethora of drug discovery and development news every month with the magazine and every day with our website.

OUT OF ORDER: SEEING THINGS

BY RANDALL C WILLIS

I REMEMBER HEARING THAT if you played a specific track on a specific Beatles album backward, you would hear someone say “Paul is dead.” I also remember almost ruining both my album and record player trying to verify this secret message.

Listening to a George Carlin album, a punchline involved someone hurling a bag of burgers toward the hapless drive-thru staff yelling “$2.52.” It was my first literal spit-take. And since that day, I see references to 252 everywhere.

Aside from indicating how old I am with the word “album,” I recount these anecdotes to highlight the idea that patterns seem to arise suddenly, and when they do, they become impossible to ignore.

More germane to DDNews, the most recent pattern I cannot seem to shake is discussion of the microbiome.

I’ve personally studied and have written about the biomolecular sciences for about 30 years. And over those three decades, I have run across a variety of endeavours and approaches that have captured the zeitgeist for a period, only to disappear several years later. I am not so old as to remember the advent of DNA sequencing (recounted in our November 2017 Special Report), but I do recall the triumphs of Clare The Human Genome Proy ect. And with its first approach to my mind’s eye, the project and its promise was suddenly trumpet blare of The Human Genome Project, only to disappear.

And over those three decades, I have run across the biomolecular sciences for about 30 years. And over those three decades, I have run across the biomolecular sciences for about 30 years. And over those three decades, I have run across the biomolecular sciences for about 30 years. And over those three decades, I have run across the biomolecular sciences for about 30 years. And over those three decades, I have run across the biomolecular sciences for about 30 years.

Listening to a George Carlin album, a punchline involved someone hurling a bag of burgers toward the hapless drive-thru staff yelling “$2.52.” It was my first literal spit-take. And since that day, I see references to 252 everywhere.

And of course, each of those approaches led to or greatly facilitated the expression of information, as each produced a glut of data that desperately needed to be turned into actionable information. To my mind, while we have become good at the data to information part, we are still challenged with “actionable.”

As an outside observer, none of these approaches existed one day and then were everywhere the next. I am confident, however, that each existed before I became aware of them, and that sudden debut was the light-switch of awareness.

Unlike my 252 scenario, however, each of these sudden appearances was partnered with a gradual disappearance.

Just as the statement “Paul is dead” is now more apt to elicit the question “Paul who?”, so too are “The Human Genome Project” and “combinatorial chemistry” likely to elicit a turn of the head.

Not that they have left us, any more than Mr. McCartney has, but rather that they have evolved into a panoply of undertakings and simply become part of the background noise of science and society.

Which brings me back to my thoughts on the microbiome.

Since writing on the topic for our January 2017 Special Report, I have seen no end of references to the microbiome in terms of human health. Most recently, in the documentary series “Island of You,” the microbiome was discussed as an explanation for food allergies.

So, the microbiome is the new Human Genome Project, combinatorial chemistry and informatics?

I may be wrong, but I think the microbiome is different.

The others were technological advances. Not to minimize the achievements, but the outcomes each offered were possible using previous technologies—they just would have been more tedious and more expensive.

The microbiome, however, is a more conceptual advance. It is a change in our thinking about biology itself. The very fact that we are struggling to “science” the microbiome, in my mind, lends it credibility as a direction worth exploring.

In some ways, John Donne was wrong; each man (and woman and child) is an island. In this case, it’s an island of a dozen or more complex ecosystems that struggle to maintain homeostasis under constant external bombardment.

To complete Donne’s sentiment, however: “No man is an island entire of itself; every man is a piece of the continent, a part of the main.” That microbiomes appear to influence each other both within and between islands bears this out.

I suspect I will continue to see mentions of the microbiome in many facings of my life in the years to come. But whereas the idea was a revelation to me, as were the others, I don’t believe this represents a sudden promulgation of drug discovery and development news every month with the magazine and every day with our website.

Randall C Willis can be reached by email at willis@ddn-news.com.
New BEAM Alliance position paper

WORLDWIDE STAKEHOLDERS called out to support SME-driven innovation and revive the product pipeline fighting antimicrobial resistance

PARIS—In 2017, the collective fight to combat antimicrobial resistance (AMR) has experienced a new upswing, according to the European BEAM alliance—and, following the eye-opening report of British economist Lord Jim O’Neill, policymakers, funding bodies and national governments set up a series of new initiatives to accelerate drug development by supporting research and development in the AMR field.

Late last year, taking advantage of the timing of World Antibiotic Awareness Week and European Antibiotic Awareness Days, the European BEAM alliance, representing 40 biopharmaceutical companies from Europe innovating in antimicrobial resistance research, released a position paper to acknowledge these efforts and to highlight the important role that small and medium-sized enterprises (SMEs) are playing as innovators.

The document lists 10 guidelines as to how antibacterial R&D could be revived and proposes specific support for SME-driven innovation in the AMR field. The alliance particularly demands that policymakers understand the specific nature and needs of SMEs to design effective “push” and “pull” mechanisms (In the funding of R&D, push mechanisms such as research grants subsidize research input, while pull mechanisms such as innovation prizes reward research output).

What BEAM is calling for:
• Adequately shaped incentive mechanisms that ultimately reward R&D evidence
• Health technology assessment recognizing the true value of SME innovation
• Dedicated regulatory pathways to support the specific needs of AMR projects and act as pre-qualification criteria to some push/pull incentive mechanisms
• Push incentives and funding mechanisms that are directed to SMEs, calibrated and accessible for SMEs in practice
• Calibrated market entry rewards to ensure continuous and sustainable innovation from academics to biotech companies and to large pharma players
• R&D prizes and phase entry rewards as effective pull mechanisms for SMEs to incentivize the most underserved indications in AMR
• Targeted tax incentives specifically addressing SMEs to incentivize private investments into AMR-focused companies and/or avoid de-prioritization
• Going beyond to exploit all possibilities for AMR from SMEs
• Support of education to strengthen attractiveness of the field for R&D professionals/scientists
• Long-term thinking and wise usage of AMR innovations combined with appropriate diagnostics development.

Marie Petit, coordinator of the BEAM alliance, says: “Existing SMEs in the AMR field are true pioneers. Despite a much undererved ecosystem to fund and perform R&D, they fight to make the difference for millions of patients and come up with very innovative approaches, both antibacterial and non-antibacterial (prevention, anti-virulence, anti-biofilm, phages, microbiome protection). They carry the hope for the coming decades, and it is of utmost importance that policymakers and countries involved in the fight against AMR make sure their policies are laser-focused on SMEs’ need and none is left behind until the ecosystem is properly revived.”

“Due to their versatile properties, bacteria are evolving resistance faster than policymakers are implementing action. It is of enormous importance to ultimately revive R&D in AMR by developing compelling surveillance data, encouraging out-of-the-box thinking, rewarding R&D evidence and strengthening existing scientific expertise,” adds Marc Gitzinger, CEO of BioVersys AG in Switzerland and vice president of the BEAM Alliance.

Marc Lemonnier, CEO of Antibio SAS in France and a member of the management board of the BEAM Alliance, comments: “Globally, some 250 biotech companies are working on new antibacterial strategies. SMEs are the crucial innovation engine in the AMR field. Addressing the specific requirements of SME-driven innovation within current AMR initiatives is key in order to provide patients with effective drugs that can win the fight against AMR.”

As part of all this effort, this month the BEAM alliance, together with Berlin-based BIOCOM AG, invited key players to a one-day conference on March 2—the 11th Berlin Conference on Life Sciences, “Novel Antimicrobials and AMR Diagnostics.” The event provided a discussion platform for addressing the specific challenges of SMEs in developing new antimicrobials and AMR diagnostics.

About the BEAM Alliance

The BEAM Alliance (Biopharmaceutical companies from Europe innovating in Anti-Microbial resistance research) plays a key role, working on a European and national level to represent the interests of its 40 members. The BEAM members are collectively developing over 120 new R&D projects focused upon the cure and prevention of bacterial infections. They cover the whole range of pharmaceutical drug development from small-molecule antibiotics, antibiotic combinations, phages, antibod-
i es, prophylactic and therapeutic vaccines, peptides, prebiotics, other bioproducts, adjunctive therapies and medical devices, thus representing the large majority of all European companies actively working on AMR. The goal of the BEAM alliance is to maintain and promote awareness of SME-driven innovation in the field and to support policymakers in understanding economic business models around AMR.

Market Insight: Therapeutic application of mAbs will increase in near future

EVER SINCE THE first commercial monoclonal antibody (mAb) was approved in 1986 for human therapeutic purposes, mAbs have been increasingly used in several areas of healthcare. According to GlobalData, a leading data and analytics company, the total number of clinical trials involving mAbs witnessed a robust 115 percent growth between 2007 and 2016.

The company’s Clinical Trials Database provides a review of company-sponsored, interventional, observational and expanded-access clinical trials of mAbs across the globe for the past 10 years from 2007 to 2016. And, says Dr. Marco Borria, senior clinical trials analyst at GlobalData: “Even though Phase 2 trials outnumbered all other trials, Phase 1 studies have grown faster than all other phases during the review period.”

During the review period, 57 percent of trials were completed, out of which 76 percent reported results. Among these, 71 percent achieved their primary endpoints.

Out of all the trials initiated, Roche has emerged as the lead sponsor, with the company’s bevacizumab as the most investigat-
ed drug. The other top industry sponsors were Novartis, Eli Lilly, Amgen, AbbVie, Pfizer, Bristol-Myers Squibb, Genentech, J&J and GlaxoSmithKline.

Oncology was the top therapy area in terms of number of clinical trials, followed by immunology, central nervous system, musculoskeletal disorders and gastrointestinal. The most common indication under investigation in these trials was rheumatoid arthritis, followed by solid tumors and non-small cell lung cancer.

There is a near-even split between multinational and single-country trials across the period. However, in the last three years multinational trials outnumbered the trials conducted in a single country. In terms of clinical trials by geographies, Europe accounted for almost 50 percent of trials, followed by North America, Asia-Pacific, South and Central America and the Middle East and Africa.

“As Phase 1 studies have proliferated more than other phases, the number of new interventions appear to be on the rise across a wider range of therapy areas and indications,” concluded Borria.
**Research & Development**

**BrieFs**

**PreveCeutical, UniQuest link up for pain treatments**

VANCOUVER—PreveCeutical Medical Inc. has begun a research cooperation agreement with the University of Queensland (UQ) Pty Limited, the main commercialization company of UQ. In conjunction with the agreement, the organizations will conduct a research program to expand the application of their disulfide linker technology and pursue development of non-addictive analgesics for alleviating pain. The multi-phase program was slated to begin March 1, led by Dr. Harendra Pandhi, UQ researcher and chief research officer of PreveCeutical, in collaboration with associate professor Peter Gabot, UQ School of Pharmacy’s pain and inflammation pharmacology expert. PreveCeutical will own all intellectual property developed under the auspices of this agreement, and will retain an option to negotiate an exclusive worldwide license to UniQuest’s background intellectual property, for which it will make milestone and royalty payments to UniQuest.

**Pfizer licenses new Genedata platform**

BASEL, Switzerland—February saw Pfizer Inc. license the Genedata Bioprocess enterprise platform from software solutions provider Genedata. Pfizer has been utilizing the Genedata Biologics platform since 2014, and integrating the two platforms will create a centralized data repository for research and development units, with better data tracking and analysis. Genedata Bioprocess is a first-in-class, off-the-shelf enterprise software solution offering fully integrated workflow support for large-molecule development and CMC. It can be operated alone or integrated with Genedata Biologics, and is a modular system that offers support from cell line development and upstream/downstream process development to formulation and analytical development.

**Protein Power**

**New methods emerge to manufacture therapeutic proteins**

BY RACHEL FLEHINGER

PHARMACEUTICAL COMPANIES across the globe are racing to bring new drugs to market, and an area of research and development that is exploding faster than most is protein-based therapeutics, which use the body’s own protein processes to design new therapies. Insulin was the first therapeutic protein to be introduced to market for the treatment of diabetes in the 1920s, and the search has been underway ever since to apply the same concept to more diseases.

The past few months have seen significant advances in the field’s promise, as two different companies have announced major breakthroughs in their ability to manufacture therapeutic proteins. A team at Chalmers University of Technology has finally mapped the metabolism of yeast cells, opening the door for mass production of critical therapies, while the UK’s Centre for Process Innovation has found a method using transgenic animals that shows remarkable promise.

Starting with the fungal angle, the Swedish Chalmers University of Technology has announced a definitive mapping of the metabolism of yeast cells, a project that took more than four years. The researchers involved chose yeast because it offers several distinct advantages as a production host—it is a fast-growing protein producer which is easy to manipulate, and which offers human-like structures that respond well to laboratory manipulation.

The production of proteins in yeast cells involves more than 100 processes and over 200 enzymes, hence the four-year process to create the comprehensive model.

**Are immortalized stem cells poor surrogates? Deleted gene that immortalizes MSCs may be critical to their function**

BY JIM CIRIGLIANO

JUPITER, Fla.—New research conducted in the lab of Dr. Donald Phinney on the Florida campus of The Scripps Research Institute (TSRI) has identified factors critical to the differentiation of mesenchymal stem cells (MSCs), which are commonly used in stem cell therapies and clinical research. The study, published in the journal Cell Death and Differentiation, suggests a new approach may be needed for how these cell lines should be treated in the lab and studied for clinical purposes.

MSCs are common tools for doctors and researchers looking to stem cell therapies to heal damaged tissue or replace dysfunctional cells. MSCs are popular because they can differentiate into a variety of mature cell types (bone, fat or cartilage, for example), and because they support the formation of blood cells (hematopoiesis) and secrete factors that promote tissue repair.

Researchers, however, oftentimes struggle to predict how primary MSCs from bone marrow will behave. Because these cells are delicate and difficult to keep alive in vitro, many scientists use immortalized MSC lines. Immortalized MSC lines are created by deleting a gene—p53—which controls the normal, programmed
Yeast is currently used in the production of insulin, as well as a therapeutic human papillomavirus vaccine that may reverse cancerous infections, but using it to manufacture protein therapies for cancer, Alzheimer’s or multiple sclerosis has proven far more challenging. Antibodies to these diseases are currently being produced in a factory that uses Chinese hamster ovary (CHO) cells as the host, a process that is extremely limited and expensive. These bio-reactors are associated with both low yield and solubility problems, making their output of limited use.

“Yeast is a superb modeling system. Almost everything in yeast is also found in humans. If we can get yeast cells to do the same thing [as CHOs], it will be significantly cheaper—perhaps 10 percent of what it costs today. Our vision is to eventually be able to mass-produce and supply the entire world with therapies that are too expensive for many countries today,” says Jens Nielsen, professor of systems biology at Chalmers University.

By studying yeast’s process step-by-step, the scientists also found mechanisms that can potentially make the process more efficient—and open doors to produce targeted antibodies in quantities that can really change the field of protein-based therapy.

Meanwhile, the Centre for Process Innovation (CPI), the UK’s technology innovation provider for process manufacturing, has been focused on creating therapeutic biologics in transgenic animals. Also recognizing the disadvantages of CHOs, they have been exploring options for other natural biological systems for protein exploration. Working in partnership with the University of Edinburgh’s Roslin Institute, researchers have worked with a line of genetically modified chickens able to express different recombinant proteins in their egg whites.

The Roslin Institute successfully created a transgenic chicken that expresses the CSF1-Fc protein—a protein that was subsequently found to markedly improve the immune system of pigs—in its egg white. The partnership will explore the ability to take egg white containing CSF1-Fc to determine the possibility for scaling the production to a level to be clinically useful in drug development.

According to their press release, the collaborators aim to demonstrate an economically viable and scalable downstream process to isolate this therapeutic protein in egg whites. Should the process prove viable and scalable, says CPI’s Natasha Lethbridge, “the next stage will be for Roslin Technologies to commercialize this protein for the reagents market.”

The implications for a faster, more efficient means of therapeutic protein development, whether through yeast or transgenic chickens, has the potential to fundamentally change biologic manufacturing. While the pharmaceutical process may take five to 10 years to bring something to market, the money-making potential for faster and more efficient commercial applications suggests that these breakthroughs will be welcome across the industry.

The Centre for Process Innovation (pictured here), in partnership with the University of Edinburgh’s Roslin Institute, has been involved with the creation of genetically modified chickens able to express different recombinant proteins in their egg whites.
Looking at cardiac cells (excluding myocytes) in unprecedented detail, researchers at The Jackson Laboratory used single-cell RNA sequencing to analyze and sort more than 10,000 cells into nine distinct categories.

The significance of these differences still needs to be empirically tested.”

Dr. Alexander Pinto, a JAX research scientist

“Whether these differences in gene expression are the basis for the sexual dimorphisms in cardiac stress responses remains to be demonstrated. The significance of these differences still needs to be empirically tested.”

Dr. Alexander Pinto, a JAX research scientist

heart. But it should be noted, in other pathology contexts, females are more susceptible to autoimmune disease such as lupus and rheumatoid arthritis.”

“We noticed genes that are implicated with inflammation are upregulated in male cells. For example, we mention Ifi8, which was recently linked to chronic inflammation. Upregulation of these genes that are linked to inflammation, with the corresponding reduction of genes linked to anti-inflammatory mechanisms, suggest the gene expression signature of certain cell types in the heart, particularly macrophages—the major sentinel of tissue damage and stress in the heart—are geared towards inflammation,” continues Pinto. “Whether these differences in gene expression are the basis for the sexual dimorphisms in cardiac stress responses remains to be demonstrated.”

The significance of these differences still needs to be empirically tested, Pinto notes, adding that the data that have been generated offer many leads to follow regarding the sex differences in injury responses observed in epidemiological and experimental studies. For example, “In granulocytes we observed an increase in pro-apoptotic genes in female cells and increase in levels of genes associated with granulocyte capacity to respond to tissue stress in granulocytes,” Pinto says. “A type of granulocytes, called neutrophils, are early infiltrators to the heart after injury and cause a lot of damage. These cells also die after they undertake their functions in the heart. Whether these cells die quicker and limit damage in female injured hearts is a possibility that needs to be explored. But many of the patterns we have identified are novel, and much work needs to be done to find out the significance of these patterns. Our findings underscore the importance of studying both female and males in context of disease and health.”

“Besides providing a much clearer picture of the cells that populate the heart, this research offers new strategies to isolate and examine some of the less-studied cell types, such as Schwann cells (cells that secrete the protective myelin sheaths along nerve axons), to determine their role in cardiovascular health and disease,” Rosenthal noted. “From our research findings we can now for the first time profile Schwann cells, vascular smooth muscle cells, pericytes and also fibroblasts with high precision using high-throughput technologies such as flow cytometry. Before this, the cell biology field was dependent on genetic approaches (for example, GFP reporters) to identify and isolate cell populations,” says Pinto. “Regarding Schwann cells, it was satisfying to see these cells clearly in our analysis. Schwann cells have not been extensively studied in context of the heart, and I think with the increased capacity to detect them, we and others have become more interested in them.”

“From a biology perspective, this research is very exciting since we can now rapidly profile an entire cellular ecosystem, and see how the different cell types in the ecosystem interact and contribute to the heart. Indeed, until recently the cellular composition of the heart was not clearly defined. Our work (published in 2016), showed that our concept of what forms the heart needed to be revised, showing that non-myocytes significantly outnumber myocytes in the heart,” finishes Pinto. “[This work] provides insights to the biology of these cells that we could not imagine not too long ago.”

Corning introduces new dissolvable microcarriers

Product offering is designed for improved large-scale cell expansion

BY DDNEWS STAFF

CORNING, N.Y.—Earlier this year, Corning Inc. expanded its microcarrier product offerings to include Corning Dissolvable Microcarriers. With the addition, the company says, scientists and technical experts seeking to avoid using harsh dissociation methods can now rely on an option for a gentler, more efficient cell harvest than is offered by traditional microcarrier technology. The company unveiled the new microcarrier offering at the Cell & Gene Therapy World in Miami, held Jan. 22-25.

“Using this material technology, these new microcarriers avoid many of the disadvantages associated with traditional microcarriers,” said Dr. Anthony Frutos, business technology director for Corning Life Sciences. “Dissociation of attached cells from the surface of traditional microcarriers can be problematic, and a subsequent separation step is required, adding complexity and cost to the overall production process. Dissolvable Microcarriers, in contrast, provide an ideal solution for applications in which functional cells are the desired product—as, for example, in cell therapy.”

Corning is one of the world’s leading innovators in materials science. For more than 160 years, Corning has applied its expertise in specialty glass, ceramics and optical physics, succeeding, the company says, “through sustained investment in R&D, a unique combination of material and process innovation and close collaboration with customers to solve tough technology challenges.” In addition to life sciences, Corning’s businesses serve the needs of consumer electronics, telecommunications and transportation, among other markets.

Large-scale cell expansion is expected to see improvements with a newly expanded microcarrier product offering from Corning Life Sciences.

“Corning’s new Dissolvable Microcarriers avoid many of the disadvantages associated with traditional microcarriers,” said Dr. Anthony Frutos, business technology director for Corning Life Sciences.
cell death (apoptosis) that occurs as a controlled part of an organism’s natural growth and development. Although initially thought to be dispensable for normal cell survival, recent studies have suggested that the gene may act as a sort of master regulator of the cells’ ability to differentiate, and that it influences not only apoptosis but also early development, reproduction, energy metabolism and hematopoiesis. This finding suggests that the dramatic effects of deleting p53 may make immortalized MSC cell lines an inappropriate surrogate for predicting the cells’ behavior in clinical applications.

"The scientific literature is replete with publications that employ immortalized cell lines as surrogates to study MSC biology," Phinney tells DDNews. "Our recent data suggest that these lines poorly recapitulate the behavior/function of primary MSCs. I believe the work will have a large impact on those scientists using rodent MSCs. We and others are also striving to delineate critical differences between rodent and human MSCs, which should aide in better translating preclinical data to the clinic."

Phinney and his team compared cells that came from normal mice against those of mice that did not express the p53 gene, and found that the level of active p53 appeared to be the primary regulating factor that determined how the MSCs differentiated. When p53 was completely deleted, the cells became immortal but developed into bone cells, losing their ability to become other types of cells. The researchers found that the gene interacts with reactive oxygen species and two transcription factors, TWIST2 and PPARG, to influence cell growth and development. A low level of p53 induced TWIST2, which discouraged any differentiation, keeping the MSCs in a stem state. A moderate level of p53 induced PPARG and reactive oxygen species, which led the cells to differentiate into fat cells rather than bone. At high levels of p53, the cells died.

"A basal level of p53 in cells in the culture is required for them to act as an accurate model for cells in the body," Dr. Veena Krishnappa, the study’s other lead author, said in a statement announcing the research’s publication.

"Our data argue that basal p53 levels are necessary for MSC self-maintenance," says Phinney. "We have shown that transient exposure to oxidative stress strongly activates p53, which results in growth arrest, reduced survival and changes in differentiation potential. Prolonged exposure leads to an increase in cellular apoptosis and selection of cells that acquire inactivating mutations in p53, which via immortalization allows rapid and sustained cell growth."

In addition to the study’s findings of the important role p53 plays in MSC differentiation, the research also suggests that inactivation of p53 may play multiple roles in the progression of bone cancers and other skeletal diseases. Inactivation of the gene may contribute significantly to tumorigenesis and tumor progression by promoting sustained cellular growth, desensitizing the cells to oxidative stress and interfering with pathways that regulate cellular differentiation.

"Mutations in p53 are known to occur at a relatively high frequency in bone cancers, and in about 90 percent of osteosarcoma patients," Phinney comments. "Efforts are underway to understand how the spectrum of p53 mutations in these tumors impact response rates to therapy, which may lead to different treatment regimens based on the tumor mutation profile. Groups are also examining downstream pathways affected by p53 mutations in the hope of identifying other potential targets for intervention."

"Our lab is interested in studying how p53 loss-of-function affects the skeletal response to obesity and mechanical unloading as a means to probe pathways that drive skeletal involution in response to these conditions," he says. 

"Our lab is interested in studying how p53 loss-of-function affects the skeletal response to obesity and mechanical unloading as a means to probe pathways that drive skeletal involution in response to these conditions," he says. 

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HBV
CONTINUED FROM PAGE 1

reverse transcriptase. They can improve liver health, but they have little effect on curing a chronic patient. A safe and effective medicine that cures the patient—no virus or viral proteins in the blood—would save this generation’s chronic HBV patients and prevent a next generation of HBV patients.”

The researchers published a study in the January 25 issue of the journal eLife explaining how the structure of the hepatitis B virus changes when bound to an experimental drug. Members of this new class of antiviral drug are now in clinical trials.

According to Zlotnick, “Our discovery suggests that this same drug could attack hepatitis B virus on multiple fronts—both preventing replication and killing new copies of the virus. If we’re smart, we can take advantage of the multiple ways this drug can work at the same time.”

A physical biochemist fascinated by virus self-assembly, Zlotnick said he started working on virus assembly as a graduate student, almost 30 years ago. The approach he took starts with fundamental biophysics that can be applied to a problem of human health. As he explained, “About half of known virus families have a spherical shell, or capsid. For hepatitis B virus, and many other viruses, you can take purified capsid protein, adjust solution conditions, and the protein will spontaneously assemble. The results usually look exactly like the native virus. After showing how we could observe HBV assembly, I became interested in how we could perturb assembly.”

He recalled that at the same time, Bayer published a paper showing that it had a drug that affected HBV in a capsid-dependent manner. While Bayer did not have a mechanism, Zlotnick’s colleague MG Finn synthesized an analog for him. They showed that the molecule sped up assembly, strengthened protein-protein interactions and interfered with normal interaction geometry.

“Since then we have been trying to get a better handle on mechanism and drug design,” Zlotnick said. “While the structure we just published is based on one particular chemical scaffold, we have developed approaches for screening chemical libraries, as have other groups, so we know there are several different chemistries that look really promising. As a group, we call the HBV assembly-activating molecules core protein allosteric modulators—CpAMs for short.”

A virus reproduces by hijacking a host’s cellular machinery to produce more of the virus. Most viruses protect their genetic material—DNA or RNA—inside the capsid. CpAMs disrupt capsid protein assembly by interfering with an enzymatic activity.

Zlotnick explained, “We are interfering with a protein-protein interaction. Normal HBV assembly is nucleated by a complex of viral RNA and reverse transcriptase. The drug can activate assembly on its own, an allosteric effect. By strengthening protein-protein interactions, they also drive more assembly and thus deplete the concentration of free core protein. By butchering normal capsid geometry, for newly assembly capsid protein and even when soaked into a pre-assembled capsid, the drug prevents the capsid from doing its job: protecting the viral genome, serving as a compartment for reverse transcription and interacting with other host and viral proteins. The HBV core protein has many functions, and so CpAMs can disrupt the assembly in the virus lifecycle.”

The IU scientists bound the CpAM to a chemical called TAMRA to make it fluorescent and easier to detect in experiments. Using cryo-electron microscopy, they found the small CpAM molecule could make the large, soccer ball-shaped virus capsid bend and distort.

“The big implication is viral capsids aren’t as impenetrable as previously thought.” Zlotnick noted. “The other implication, which may be even more important, is that if this type of interference works against hepatitis B virus, it might also work against other viruses. About half of known virus families have soccer ball-like capsids; examples include polio and herpes.”

Adam Zlotnick of Indiana University

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IIT’S NOT AS IF SCIENCE ever really stops being active; to be honest, it often seems more like it doesn’t know how to slow down. And one of the areas where that seems to be the case more than most is in cancer research. Not surprising, really, when one considers how ubiquitous and intractable a health problem it has been for so long.

As much of a scourge as cancer remains worldwide, the ability to fight back against tumors has vastly improved, and new strategies have been emerging with much gusto and sometimes great speed in recent years.

A chance to get a good look into the work of oncology research presents itself once again this year thanks to the American Association for Cancer Research (AACR), which will hold its AACR Annual Meeting 2018 from April 14 to 18 at McCormick Place North/South in Chicago.

And, as AACR notes on its meeting website, “Since the last annual meeting, we have witnessed another dramatic wave of progress against cancer, from exciting basic science findings to new drug approvals, expanded use of genomic data for precision medicine and a greater focus on “big data” to accelerate progress in cancer research and in the clinic. Scientists are harnessing the power of mathematics, engineering and artificial intelligence to diagnose cancer at an earlier stage. They are also concentrating their efforts on cancer in minorities and the medically underserved, working to eliminate the persistent disparities in cancer outcomes.”

The theme for the meeting, “Driving Innovative Cancer Science to Patient Care,” reflects all of this and, as AACR notes, “As we wind down our 110th anniversary year, this theme is a powerful reminder that at the heart of every scientific advance is a patient in urgent need of a cure.”

Presentations at the meeting will cover the latest basic, translational, clinical and prevention-focused research in the field, including important areas such as early detection, cancer interception and survivorship in all populations. AACR will feature new sessions on cancer health disparities that have been inspired by one of the association’s presidential initiatives, and AACR will be bringing back a popular new feature from last year’s meeting—“Unsolved Mysteries”—which features provocative questions and their in-depth discussion by speakers and members of the audience.

For more about the upcoming AACR 2018 meeting, DDNews spoke to AACR Annual Meeting Program Committee Chair Dr. Elaine R. Mardis, who is co-executive director of the Institute for Genomic Medicine and professor of pediatrics at Nationwide Children’s Hospital in Columbus, Ohio.

The opening ceremony for last year’s annual meeting of the American Association for Cancer Research.

DDNews What’s new this year or altered? What was the rationale/reason and what is the benefit?

Dr. Elaine R. Mardis: In principle, content is altered year-to-year because we want to reflect the newest breakthroughs in basic cancer and translational/clinical cancer research. This year, we generally are reflecting the impact of technology on cancer science. We have specific areas of focus on 1) “convergence,” which basically refers to the application of computational, mathematical, engineering and physics-based methodologies to cancer research; 2) survivorship as an emerging discipline in cancer medicine; 3) basic cancer science and clinical trials results for the newest types of immunotherapies and other targeted therapies; and 4) liquid biopsy applications and results.

The reasoning behind these broad-based content aspects is that they reflect emergent areas in cancer research and translational medicine today that are (importantly) pertinent to our attendees’ interests. As such, attendees benefit from learning about new developments, with an opportunity to explore areas of basic and applied cancer research that may be outside of their typical interest areas, if desired. Given the breadth and types of cancer studies and cancer medicine these days, it is really difficult to achieve content that absolutely is inclusive, but we certainly do try.

Regarding specific sessions, one new offering this year is a panel discussion of survivorship that is meant to elucidate this emerging discipline in cancer medicine, and to inform attendees about the importance of survivorship-based research and clinical practice. Also, although cancer health disparities is a topic that is carried throughout the meeting, four sessions focus solely on aspects of...
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Evaluate relevant biomarkers.
AACR News: Johnson & Johnson Lung Cancer Innovation Science Grants

PHILADELPHIA — The American Association for Cancer Research (AACR) has announced the launch of the AACR-Johnson & Johnson Lung Cancer Innovation Science Grants to stimulate research aimed at eradicating the devastating disease. This new funding opportunity, which is supported by the Johnson & Johnson Lung Cancer Initiative, is focused on “igniting scientific innovation and transformational advances against lung cancer.”

A total of $4.5 million will be made available in research funding in support of meritorious research projects. Three multi-institutional research teams that seek novel approaches to the prevention, interception and cure of lung cancer will each be awarded up to $1.5 million over a period of three years. The deadline for submission is Wednesday, May 2, at 1 p.m. Eastern Standard Time. Research projects will begin on July 1, 2018.

“Lung cancer is the leading cause of cancer death worldwide, and more research is urgently needed if we are to markedly reduce incidence and mortality from this complex disease. These grants will identify innovative strategies to eliminate behaviors that increase lung cancer risk, devise new ways to intercept a lung cancer-causing process before lung cancer occurs and develop effective treatments that offer the potential for a cure,” said Dr. Margaret Foti, CEO of the AACR.

Proposals submitted for this funding opportunity should consider the concepts that lung cancer is often caused by behaviors that lead to: chronic exposure to respiratory carcinogens that produce cellular/genomic damage; chronic inflammation; alterations in innate and adaptive immunity; and changes in the pulmonary microbiome. Consequently, these events may trigger the escape of transformed cells from immune surveillance. Proposals that characterize premalignant lesions or that substantially improve the detection of lung cancer at more curable stages will also be prioritized for funding.

Grant applications will be accepted from multi-institutional teams, composed of principal investigators from at least two, but no more than three, different institutions. Recipients will be notified by June.

Applications must be submitted using the proposalCENTRAL website. Further details are available online at the AACR website at www.aacr.org. Additional inquiries may be directed to the AACR’s Scientific Review and Grants Administration department, at grants@aacr.org.

AACR CEO Dr. Margaret Foti is pictured here, speaking during the 2017 annual meeting of the American Association for Cancer Research.
Cancer Genomics Research
Immune Therapy
Immunogenomics and Resources for Computational Methods and Mistakes in Cancer Screening in LMIC Roundtable Discussions
Nonimmunologists: Cancer Immunology for Nonimmunologists
Therapies in Thyroid Cancer
Cancer Genomics to Targeted Intratumoral Heterogeneity
Cancer Evolution: Biologic Topics of Interest
Biosimilars in Oncology: Key Analysis
AI Methods for Cancer Oncology
Basket Trials for Precision
Autophagy in Cancer Therapy
Nucleic Acids Sensing
Immunity on the Road to Autoimmunity Meets Tumor Advances in Cancer Vaccines
Immunotherapeutic Approaches to Pediatric Solid Malignancies
Cancer Drug Discovery and Multifactorial Cancer Drug Targets
Frontiers in Personalized Immunotherapy of Hematologic Malignancies
Genetic, Epigenetic, and Cellular Context Driving Pediatric Brain Hijacking the Epigenome in Cancer: Challenges and Opportunities
Impact of the Microbiome in Cancer Immunity
Metabolic Landscapes and Reprogramming for Cancer Therapy
Convergence of Theoretical Physics Approaches to Cancer
Co-stimulation and Co-inhibition in T Cell-Mediated Immunity
Development of Brain Penetrant Inhibitors: From Genomics to the Clinic
From Chemistry to the Clinic: Part 1 - Chemical Probes for Identifying and Validating Drug Targets
From Chemistry to the Clinic: Part 2 - Lead Optimization in Cancer Drug Discovery and Development, Multifactorial Optimization from Early Hits to Drug Candidates
From Chemistry to the Clinic: Part 3 - Approaches to Drug Design for Neuro-oncology
Pancreatic Cancer Prevention
Predictors and Mechanisms of Success or Failure of Immunotherapy
Quantitative Methods for Characterization of Tumor Evolution
Recent Advances and Opportunities in Small Cell Lung Cancer (SCLC) Research
Response and Resistance to CDK4/6 Inhibitors in Breast Cancer
Rethinking Immunotherapeutic Approaches to Pediatric Solid Malignancies
Revisiting Vitamin C as an Epigenetic Therapeutic
RNA Metabolism in Cancer
Single-Cell Analysis of the Cancer Epigenome and Transcriptome
Translational Control of Cancer
The Use and Abuse of Chemical Probes: Ensuring Best Practice for Interrogating Biology and Target Validation
What Can We Learn about Cancer by Combining Germline and Somatic Data?

EDUCATIONAL SESSIONS SATURDAY, APRIL 14, 2018

Advances in Cancer Vaccines
Autoimmunity Meets Tumor Immunity on the Road to Nucleic Acids Sensing
Autophagy in Cancer Therapy
Basket Trials for Precision Oncology
Big Data, Deep Learning, and AI Methods for Cancer Analysis
Biosimilars in Oncology: Key Topics of Interest
Cancer Evolution: Biologic Clinical Significance of Intratumoral Heterogeneity
Cancer Genomics to Targeted Therapies in Thyroid Cancer
Cancer Immunology for Nonimmunologists
Cancer Immunology for Nonimmunologists: Roundtable Discussions
Cancer Prevention and Screening in LMIC
Common Statistical Errors and Mistakes in Cancer Research: How to Avoid Them
Computational Methods and Resources for Immunogenomics and Immune Therapy
Computational Methods for Cancer Genomics Research

Thousands will be in Chicago for the AACR 2018 annual meeting, offering many opportunities for learning, collaboration and sharing, networking and just catching up with friends and colleagues, just as at previous meetings like this one in 2017.

AACR 2018 Cancer and Biomedical Research Career Fair
Saturday, April 14, 2018 9:00 a.m. – 3:30 p.m.

AACR extends an invitation to all scientists to attend its 2018 Cancer and Biomedical Research Career Fair in Chicago on April 14. A special invitation is extended to mid-career scientists to join AACR at this premier recruiting event. Recruiters from academia, government and the pharmaceutical industry will be available to meet with individual scientists throughout the fair.
Meet the Research Icon Sessions
Organized by the Associate Member Council (AMC) See the Online Itinerary Planner for dates and times
These sessions are intended for early-career scientists and provide a special opportunity for young investigators to meet esteemed researchers in a small group setting to discuss their specific career paths and visions for the future of cancer research. Sessions take place in the Associate Member Resource and Career Center in AACR Central.

Career Discussions
Organized by the Associate Member Council (AMC) See the Online Itinerary Planner for dates and times
These informal networking and discussion sessions are designed for early-career scientists to interact with junior faculty and physician scientists. Sessions take place in the Associate Member Resource and Career Center in AACR Central.

Personalized Career Conversations
Co-sponsored by the Associate Member Council (AMC), Minorities in Cancer Research (MICR) and Women in Cancer Research (WICR), Saturday, April 14, 2018
3:30 p.m. – 5:00 p.m.
This session provides a unique opportunity for early-career AACR Associate Members to be paired with distinguished cancer researchers for one-on-one conversations. There is no cost to participate in this session, but preregistration is required. Preregistration and a list of this year’s participating senior scientists will be available shortly (March 2018).

10th Annual Careers in Clinical and Translational Cancer Research Roundtable
Organized by the Clinical and Translational Cancer Research Committee, Saturday, April 14, 2018
This annual session will include a series of presentations by recognized leaders in clinical and translational cancer research, followed by informal roundtable discussions. Participating senior investigators will provide attendees with personal perspectives with regards to their own career paths in an effort to help direct aspiring clinical and translational cancer researchers on successful career paths.

Navigating the Road to a Successful Career in Cancer Research
Organized by the Minorities in Cancer Research (MICR) Council, Monday, April 16, 2018
6:30 p.m. – 8:30 p.m.
This session provides a forum in which students, postdoctoral candidates and junior faculty can discuss career development issues with established senior scientists. This session includes a networking reception and mentored roundtable discussions facilitated by senior researchers representing all sectors of the cancer community, including academia, government and industry.

WICR Professional Advancement Session
Organized by the Women in Cancer Research (WICR) Council, Saturday, April 14, 2018
1:00 p.m. – 3:00 p.m.
The WICR Professional Advancement Session provides a forum for investigators to acquire skills and techniques to enhance their careers. Participants are led by role models and through guided exercises that enable them to learn key concepts. Past topics have included: Intentional Yes and Graceful No: How to Take Charge of Your Career, Thriving in an Overworked World, The Power of Assertiveness, The Art of Engaging in a Successful Interview, and Building Presence and Leadership through Empowered Communication.

WICR Career Mentoring Session
Organized by the Women in Cancer Research (WICR) Council, Monday, April 16, 2018
8:15 a.m. – 10:15 a.m.
Following a keynote address, attendees will have the opportunity to meet, network and learn from many of the leading senior scientists in cancer research during roundtable discussions. Topics of discussion will include work-life integration, careers in industry, choosing a postdoctoral position, oral presentations and more.

The Critical Role of Physician-Scientists in Advancing Cancer Science: Suggestions for Continued Success
Professional Advancement Session
Organized by the AACR Science Education and Career Advancement Committee, Friday, April 13, 2018
5:30 p.m. – 7:00 p.m.
Physician-scientists serve several crucial roles by relating scientific discoveries in cancer to the clinical care of patients and/or the health of populations, and vice-versa. In these roles, physician-scientists contribute to the advancement of cancer science through research, clinical care, education/mentoring and/or administrative leadership across the course of their careers. Often they serve at crucial translational interfaces between scientific discoveries that develop into newly approved devices, drugs or guidelines to benefit patients. Additionally, physician-scientists often serve as interpreters or translators to describe the relevance, importance and impact of science and scientific discoveries to patients and the broader public. As grant funding opportunities narrow, physician-scientists’ competitiveness versus “scientifically focused” colleagues can be threatened. Similarly, as fiscal margins associated with cancer care come under greater pressure due to numerous internal and external forces (e.g., narrowing insurance networks, rising costs of cancer care, growing use of EHRs), physician-scientists come under increasing pressure to care for larger numbers of patients of greater complexity, often placing additional restrictions on time. This session will explore the critical role of physician-scientists and strategies for their continued success in the face of increasing competitiveness in all domains of their professional service—scientific, clinical, educational and administrative.

13th Annual Undergraduate Student Caucus and Poster Competition
Organized by the AACR Science Education and Career Advancement Committee, Saturday, April 14, 2018
10:00 a.m. – 4:00 p.m.
With over 250 undergraduate student participants every year, the Undergraduate Student Caucus Poster Competition continues to be the premier event for undergraduate students attending the AACR Annual Meeting. Now in its thirteenth year, this session gives undergraduates the opportunity to learn more about current research in the cancer field, hear from investigators about educational pathways and career development, explore career options in the cancer field and compete for monetary prizes while presenting research. Undergraduates at all levels as well as post-baccalaureate students are welcome to participate without cost. AACR members are encouraged to volunteer as judges.

Meet the Mentor: Undergraduate Focus I and II
Organized by the AACR Science Education and Career Advancement Committee, Sunday, April 15, 2018
3:45 p.m. – 4:45 p.m.
These sessions feature esteemed senior scientists who will engage undergraduate students in informal discussions about cancer research. Sessions are intended to help guide students in their educational pursuit of establishing a career in cancer research. All undergraduate student attendees at the Annual Meeting are encouraged to participate.

Special Program for High School Students: The Conquest of Cancer and the Next Generation of Cancer Researchers
Organized by the AACR Science Education and Career Advancement Committee, Tuesday, April 17, 2018
8:30 a.m. – 2:30 p.m.
This interactive program is designed to inspire students to pursue careers in cancer research and biomedical sciences by providing an opportunity for students to learn about cancer from cancer research experts while interacting with their peers. The program includes lectures, tours of the exhibits and poster areas, student presentations and a networking lunch. AACR members are encouraged to volunteer as judges.
Eureka! Have we found it?

Research institutes use their prowess to help unlock discoveries for cancer treatment targets and pathways

BY JEFFREY BOULEY

The thrill of discovery for humans goes way back, before the existence of the state of California (where I did most of my growing up) and its adoption of “Eureka” as the state motto—probably related to the discovery of gold there. Even millennia before the ancient Greeks, from whom we derive the word “Eureka,” which literally means “I found it,” and is an exclamation associated with discovery and invention, and often attributed to Ancient Greek mathematician and inventor Archimedes. And it certainly goes inconceivably far back before the early days of this magazine, when we were named Drug Discovery News and that was the part of the pharmaceutical research and development pipeline on which we truly focused.

So, even as we honor the upcoming American Association for Cancer Research annual meeting (a preview of which appears in this issue) by running this special sec-

A step toward stopping metastasis

Scientists at the La Jolla, Calif., campus of The Scripps Research Institute (TSRI) released news of recent research they have conducted that could offer a leg up for efforts to target tumors before they metastasize.

The study, published recently in the Nature research journal Oncogene under the title “LTBP3 promotes early metastatic events during cancer cell dissemination,” shows that a protein called Latest LTBP3 Binding Protein 3 (LTBP3) is the driver behind a “chain reaction” that leads some early developing tumors to grow new blood vessels—vessels which then become the pathways for spreading cancer cells throughout the body and setting the stage for metastasis early on.

“Lower LTBP3 levels appear to be associated with better prognosis in patients with certain types of cancer,” says Dr. Elena Deryugina, an assistant professor at TSRI and first author of the new study. Deryugina led the collaborative study with senior authors Dr. James P. Quigley, a TSRI professor, and Dr. Daniel Rifkin, a professor at the New York University School of Medicine.

According to TSRI, their research addresses a long-standing challenge in medicine, explaining that over the years, a potent growth factor molecule called TGFβ has become an area of high interest for many researchers in the oncology field. The reason? In a good cop/bad cop manner, TGFβ plays multiple roles in health and disease—specifically, it can be both a promoter and suppressor of tumor cell growth.

The problem, though, is that while TGFβ seems a promising cancer therapy target, researchers haven’t been able to figure out how to dampen its harmful effects without interfering with its normal roles in the body.

TSRI notes that, as long-time collaborators, Deryugina and Quigley have led research that shows the initial steps of tumor metastasis can occur when a primary tumor is barely detectable. This work sparked their interest in the role of LTBP3 because they knew that LTBP3 partners with TGFβ to regulate its secretion, activation and maturation, but wondered what else LTBP3 might control. For example, could LTBP3 set TGFβ on its harmful path of action in early-stage tumors, and might LTBP3 have its own role, independent of TGFβ, in cancer metastasis?

The TSRI-led research used chick embryo tumor models and a rodent model of head and neck cancer to discover how LTBP3 is involved in the spread of aggressive tumor cells. They knocked down LTBP3 expression and secretion in human tumor cell lines representing carcinoma, head and neck carcinoma and a fibrosarcoma. In each model, the team found that without LTBP3, primary tumor cells could not metastasize efficiently.

“Our experimental findings showed that LTBP3 is active in the very early steps of metastatic spread,” said Quigley.

“Specifically, LTBP3 appears to help tumors grow new blood vessels in a process called angiogenesis, which is critical for tumor cell intravasation. That is when cancer cells enter into blood vessels of defined size and permeability,” added Deryugina.

Importantly, the new data is in line with clinical findings that LTBP3 levels can indicate better overall survival in cancer patients with early-stage head and neck carcinomas. Taken together, these findings suggest LTBP3 may be a cancer immunotherapy target.

Vedanta expands network supporting microbiome therapeutics for cancer immunotherapy work

CAMBRIDGE, Mass.—Vedanta Biosciences late last year announced new translational medicine collaborations in cancer immunotherapy with Leiden University Medical Center and the University of South Alabama Mitchell Cancer Institute, and it also announced the expansion of its translational medicine collaboration in cancer immunotherapy with NYU Langone Health and its Perlmutter Cancer Center.

Researchers at these institutions have been collaborating with Vedanta Biosciences to analyze microbiome clinical data from interventional checkpoint inhibitor studies to identify microbiome signatures associated with response to immunotherapy and key mechanisms through which the gut microbiota modulate immunotherapeutic responses.

“Data from our ongoing clinical collaborations in melanoma show that gut bacteria signatures could help determine if a cancer immunotherapy will work,” said Dr. Bruce Roberts, who is the chief scientific officer of Vedanta Biosciences. “We’re pleased to expand our research collaborations into other forms of cancer, with the ultimate goal of identifying ways to change the microbiome to increase the proportion of patients and types of cancer patients who respond to immunotherapies.”

Vedanta Biosciences’ immunoncology programs include lead product candidate VE800, which has been shown in preclinical models to activate CD8+ T cells, improve CD8+ T cell tumor infiltration and improve survival in several cancer models in combination with checkpoint inhibitors. Vedanta anticipates filing an Investigational New Drug application for this candidate in 2018.

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

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EUREKA
CONTINUED FROM PAGE 26

Given this dynamic, it is unsurprising that past researchers have explored compounds to activate REV-ERBs in an effort to treat various metabolic disorders by halting fat synthesis. But taking a wholly different path, Panda and his colleagues decided to examine whether activating REV-ERBs would slow cancer growth, since cancer cells rely heavily on the products of both fat synthesis and autophagy to grow.

“While current cancer research was investigating established cancer hallmarks/characteristics, we decided to explore something completely new,” said Gabriele Sulit, a Salk research associate and the paper’s first and co-corresponding author. “Given the importance of the circadian clock in the regulation of many cellular and physiological processes, we hypothesize that targeting the circadian clock with drugs may open up a way to novel anticancer strategies. This study is very exciting because it sheds light on a new uncharacterized way to treat cancer with very limited toxicity.”

“We’ve always thought about ways to stop cancer cells from dividing,” added Panda. “But once they divide, they also have to grow before they can divide again, and to grow they need all these raw materials that are normally in short supply. So cancer cells devise strategies to escape the daily constraints of the circadian clock.”

Although cancer cells contain REV-ERB proteins, somehow they remain inactive. Panda’s team used two REV-ERB activators that had already been developed—SR9009 and SR9011—in studies on a variety of cancer cells, including those from T cell leukemia, breast cancer, colorectal cancer, melanoma and glioblastoma. In each cell line, treatment with the REV-ERB activators was enough to kill the cells. The same treatment on healthy cells stop cancer cells from dividing,” added Panda. “That makes sense because irrespective of where or how a cancer started, all cancer cells need more nutrients and more recycled materials to build new cells.”

The researchers then tested the drugs on a new mouse model of glioblastoma recently developed by Indra Verma, a professor in the Salk Institute’s Laboratory of Genetics. Once again, the REV-ERB activators were successful at killing cancer cells and stopping tumor growth, but seemed not to affect the rest of the mice’s cells. Verma says the findings are exciting not only because they point toward existing REV-ERB activators as potential cancer drugs, but also because they help shine light on the importance of the link between the circadian cycle, metabolism and cancer.

The rest of the time, higher levels of REV-ERB proteins are responsible for turning on and off metabolic processes so that the cells are not flooded with excessive fat synthesis and recycled nutrients. As REV-ERBs are responsible for turning on and off cells’ ability to synthesize fats, as well as their ability to recycle materials—a process called autophagy—throughout the day.

In healthy cells, fat synthesis and autophagy are allowed to occur for about 12 hours a day when REV-ERB protein levels remain low. The rest of the time, higher levels of the REV-ERB proteins block the processes so that the cells are not flooded with excessive fat synthesis and recycled nutrients.

The circadian cycle, the intrinsic clock that exists in all living things, is known to help control when individual cells produce and use nutrients, among many other functions. As Salk notes, scientists previously discovered that proteins known as REV-ERBs is lethal in cancer and oncological processes, we hypothesize how healthy cells use a 24-hour cycle to regulate the production of nutrients.

“When we block access to these resources, cancer cells starve to death but normal cells are already used to this constraint, so they’re not affected,” said Dr. Satchidananda Panda, a professor in the Salk Institute’s Regulatory Biology Laboratory and lead author of the paper.

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Cell lines to accelerate cancer therapies

Concluding with something research- and discovery-oriented but not in the realm of published studies, we have news from late last year that the Philadelphia-based Gene Editing Institute of Christiana Care’s Helen F. Graham Cancer Center & Research Institute signed an agreement to provide genetically modified cell lines to Analytical Biological Services Inc. (ABS) of Wilmington, Del., to help speed up the development of next-generation cancer therapies.

Under a three-year agreement, the Gene Editing Institute will act as sole provider of gene-editing services and genetically modified cell lines to ABS for replication, marketing and distribution to leading pharmaceutical and biomedical research companies worldwide.

“This agreement with ABS will speed the progress in the discovery of effective cancer therapies and accelerate the path to prevention, diagnosis and treatment of many forms of cancer,” said Dr. Nicholas J. Petrelli, the Bank of America endowed medical director of the Helen F. Graham Cancer Center & Research Institute.

“This partnership greatly enhances our capability to provide the highest-quality genetically engineered cells for drug discovery,” Dr. Charles Saller, ABS president and CEO, commented in a press release. “Our partners at the Gene Editing Institute are advancing molecular medicine, and their expertise adds a new dimension to our efforts to speed up drug discovery.”

“One goal of The Gene Editing Institute is to develop community partnerships that can advance translational cancer research,” added Dr. Eric Kmiec, founder and director of the Gene Editing Institute. “The Gene Editing Institute is driving innovation in gene engineering, and ABS has the know-how to grow and expand the cells in sufficient quantities, as well as to market them to pharmaceutical and biotechnology clients for drug screening and research.”

The Gene Editing Institute is one of the leaders in designing the tools that scientists need to manipulate and alter human genetic material more easily and more efficiently. Last year, scientists at the Gene Editing Institute described in the journal Scientific Reports how they combined CRISPR and short strands of synthetic DNA to greatly enhance the precision and reliability of the CRISPR gene editing technique. Called Excision and Corrective Therapy, or EXACT, this new tool acts as both a Band-Aid and a template during gene mutation repairs.

By inactivating a single gene, scientists can test if it affects tumor formation or somehow alters the response to cancer therapies. Similarly, inserting a gene into a cell can produce a gene product that is a target for potential new drugs.

“Gene editing and the CRISPR technology is having a major impact on anticancer drug development because it allows us to validate the target of the candidate drug,” Kmiec remarked. “Pharmaceutical companies want to use gene-editing tools to identify new targets for anticancer drugs and to validate the targets they already have identified.”

REV-ERBs have been an area of interest for researchers looking to treat metabolic disorders by blocking fat synthesis, but they may also have an application for starving cancer cells without harming normal cells, according to researchers at the Salk Institute.
Tumors on trial
A roundup of recent clinical trial updates in the oncology realm

BY DDNEWS STAFF
CAMBRIDGE, Mass. & BEIJING—BeiGene Ltd., a commercial-stage biopharmaceutical company focused on developing and commercializing molecularly targeted and immuno-oncology drugs for the treatment of cancer, presented preliminary clinical data from patients with urothelial carcinoma (UC) enrolled in an ongoing Phase 1 clinical trial of tislelizumab, an investigational anti-PD-1 antibody, at the 2018 Genitourinary Cancers Symposium in San Francisco in February.

The preliminary Phase 1 data suggest that tislelizumab was generally well tolerated and exhibited objective responses in patients with UC.

“Tislelizumab is currently being evaluated in five pivotal trials globally and in China, including a pivotal trial in patients with previously treated, PD-L1-positive, locally advanced or metastatic urothelial carcinoma in China. This is the first presentation of tislelizumab data in the population with urothelial cancer, an area of unmet need. We are pleased by these preliminary results, which we believe provide an important foundation for our clinical understanding of tislelizumab’s efficacy and safety in specific patient populations both as a single agent and in combination,” commented Dr. Amy Peterson, chief medical officer for immuno-oncology at BeiGene.

Tyme tackles prostate cancer
SAN FRANCISCO—Tyme Technologies Inc., a clinical-stage biotech that was also presenting at the 2018 Genitourinary Cancers Symposium, announced efficacy and safety data from an ongoing Phase 2 trial of SM-88 in patients with non-metastatic, biochemical-recurrent prostate cancer (nmPC).

“Prostate cancer patients have limited treatment options and are likely to receive ADT (androgen deprivation therapy), a hormone therapy that lacks sufficient evidence of efficacy in non-metastatic prostate cancer and may produce considerable toxicities and a reduction in quality of life,” said Dr. Mack Roach III, a professor of radiation oncology and urology at the University of California, San Francisco. “Toxicities typically associated with ADT have not been seen with SM-88, which suggest that ADT may be avoided or delayed without progression in patients with non-metastatic prostate cancer. I look forward to continuing to work with Tyme to explore the benefits of SM-88 as an alternative to hormone therapy in prostate cancer patients, particularly those pursuing active surveillance.”

Currently, 73 percent of patients (121/333) have maintained radiographic progression-free survival (pPFS) with a median of 12 months since documented biochemical recurrence, and 10 months since starting SM-88 treatment. “Our data suggest that SM-88 is an alternative to hormone therapy in prostate cancer patients, particularly those pursuing active surveillance,” commented Dr. Amy Peterson, chief medical officer for immuno-oncology at BeiGene.

Array against melanoma
BOULDER, Colo. & CASTRES, France—Array BioPharma Inc. and Pierre Fabre in February announced results of the planned analysis of overall survival (OS) from the pivotal Phase 3 COLUMBUS trial in patients with BRAF-mutant melanoma. Treatment with the combination of encorafenib 450 mg daily and binimetinib 45 mg twice daily (COMBO450) reduced the risk of death compared to treatment with vemurafenib 960 mg twice daily. Median OS was 31.6 months for patients treated with COMBO450, compared to 16.9 months for patients treated with vemurafenib as a monotherapy.

“Many patients with BRAF-mutant melanoma still face significant challenges managing their disease, and there remains a substantial need for well-tolerated treatments that delay disease progression and improve overall survival,” said Dr. Keith T. Flaherty, director of the Termeer Center for Targeted Therapy at Massachusetts General Hospital Cancer Center and professor of medicine at Harvard Medical School. “This data suggests that the combination of encorafenib and binimetinib may have the potential to become a meaningful new therapy for patients with advanced BRAF-mutant melanoma.”

Genentech confronts kidney cancer
SOUTH SAN FRANCISCO, Calif.—Genentech, a member of the Roche Group, recently announced results from the positive Phase 3 IMmotion150 study of Tecentriq (atezolizumab) and Avastin (bevacizumab) as a first-line treatment for advanced or metastatic renal cell carcinoma. The study met its co-primary endpoint of investigator-assessed progression-free survival (PFS) in people whose disease expressed the PD-L1 (programmed death-ligand 1) protein. Those who received Tecentriq plus Avastin had a 26-percent reduced risk of disease worsening or death compared to people treated with sunitinib (median PFS: 11.2 vs. 7.7 months). Initial observations from the co-primary endpoint of OS in the overall study population (intention-to-treat) were encouraging, but are still immature. Safety for the Tecentriq and Avastin combination appeared consistent with the known safety profile of the individual medicines and what was previously reported in the Phase 2 IMmotion150 study.

“This is the second positive Phase 3 study that includes Tecentriq and Avastin as part of a treatment regimen, providing further evidence to support the potential of this unique combination,” said Dr. Sandra Horning, chief medical officer and head of global product development.

Two trials provide lymphoma hope
HEIDELBERG, Germany—Feb. 1 saw Affimed N.V., a clinical-stage biopharmaceutical company focused on highly targeted cancer immunotherapies, report additional preliminary patient data from two separate clinical studies of its lead NK cell engager candidate AFM13. The data demonstrate that AFM13 was well tolerated and showed promising therapeutic efficacy both in combination with the anti-PD-1 antibody Keytruda (pembrolizumab) in Hodgkin lymphoma and as a monotherapy in CD20-positive lymphoma.

“We are extremely encouraged by these new data, which indicate that the first-in-class NK cell engager AFM13 has achieved clinically meaningful responses both as single agent and in combination with a checkpoint inhibitor,” said Dr. Adi Hoess, CEO of Affimed. “In particular, in our combination trial with Keytruda, we are excited to have increased both overall and complete metabolic response rates.”

New MOA for Aptamer with therapeutic potential against NHL
IRVING, Texas—Caris Life Sciences was recently involved in a data presentation at the 59th American Society of Hematology Annual Meeting & Exposition in Atlanta, demonstrating the identification of a new mechanism of action to treat non-Hodgkin lymphoma (NHL). “We are extremely encouraged by these new data, which indicate that the single-stranded DNA aptamer Cto36 specifically binds to heterogeneous nuclear ribonucleoprotein U (hnRNP U), a protein that controls pre-mRNA splicing, which is a highly dynamic process enabling cells to rapidly adjust to changing conditions by creating a range of mRNA variants that encode different proteins.

Cancer cells frequently display splicing regulatory factors, such as heterogeneous nuclear ribonucleoproteins on their surface, and show broad dysregulated pre-mRNA splicing. If the splicing machinery is disrupted, it is believed “splicing chaos” may occur leading to cell death.

Results of this study showed that Cto36 binding to cell-surface hnRNP U resulted in internalization of the complex, disruption of pre-mRNA splicing and cell death in a subset of NHL cell lines in vitro. The authors concluded that the aptamer, Cto36, binds to hnRNP U and kills NHL cells via a novel mechanism of interfering with pre-mRNA splicing.

“This paper further validates the capabilities of our aptamers to not only identify biomarkers for use in diagnostics and drug development, but also to identify new pathways and therapeutic candidates that impact them. Using the Adapt Biotargeting System, we can create and identify thousands to millions of synthetic molecules and targets simultaneously,” said Dr. David Spetzler, president and chief scientific officer of Caris.

“Our next steps are to continue to characterize the breadth of activity of Cto36 across various cancer cell lineages and to prepare for further validation in vivo.”

For more information, visit www.DDN-News.com
Eisai enters into licensing deal with Adlai Nortye

TOKYO—January saw Eisai Co. Ltd. announce that it had entered into a licensing agreement granting exclusive rights concerning the research, development, manufacture and marketing of Eisai’s in-house discovered potential anticancer agent E7046, which is an investigational prostaglandin Ez (PG Ez) type EP4 receptor antagonist, to Adlai Nortye Biopharma Co. Ltd. in all regions outside of Japan and part of Asia (excluding China).

E7046 is an orally administered, selective EP4 receptor antagonist discovered by Eisai’s U.S. Andover research facility. It is suggested that PG Ez signals through EP4 receptors may suppress the antitumor activity of immune cells. By inhibiting EP4, E7046 is expected to act on the tumor microenvironment via a different mechanism to immune checkpoint inhibitors to potentially demonstrate antitumor effects.

Currently, E7046 is being investigated as a monotherapy in a Phase 1 clinical study as well as a Phase ib clinical study in combination with radiotherapy/chemoradiotherapy.

Adlai Nortye is a science-led clinical-stage biopharmaceutical company dedicated to discovering, developing and commercializing new and effective immunotherapies for patients with cancer. Eisai positions oncology as a key therapeutic area, and is aiming to discover revolutionary new medicines with the potential to cure cancer. By licensing E7046 to Adlai Nortye, which is developing several tumor immunotherapies that have synergies with E7046, Eisai aims to maximize the value of the agent in order to hopefully contribute to the treatment of patients in the future who need tumor immunotherapies as soon as possible.

Speeding up timelines for CAR-T trials

SHANGHAI & CUPERTINO, Calif.—Cellular Biomedicine Group Inc. (CBMG), a clinical-stage biopharmaceutical firm engaged in the development of immunotherapies for cancer, recently announced its plan to configure part of its facility in Shanghai with GE Healthcare’s FlexFactory platform, which will be designed to speed up manufacturing timelines for its cell therapy clinical trials and commercial launch.

“This is a productivity revolution in the CAR-T space—this new generation of semi-automated and standardized CAR-T manufacturing capabilities created by GE Healthcare and CBMG may allow cell therapy to provide an optimal platform and opportunity for general oncology patients. This long-term collaboration with GE could help us utilize digital technology, semi-automation and analytics, in an effort to reduce overall costs and deliver treatments to patients more efficiently,” said Tony (Bizuo) Liu, CEO of CBMG.

GE Healthcare’s FlexFactory solution will support CBMG by providing process development and training services, cell processing equipment, semi-automation capabilities and digital connectivity solutions—all of which support current good manufacturing practices (cGMP)-compliant manufacturing. CBMG plans to use its FlexFactory to speed up its timelines for commercializing its CAR-T cell therapies, targeting various blood and solid tumor cancers.

“As the rate in which cell therapies are moving through clinical trials, we understand how critical it is for companies to scale out manufacturing process capabilities, while still meeting clinical development timelines and remaining cost effective. We are committed to collaborating with cell therapy manufacturers on their journey from trials to commercialization, as they look to ultimately deliver these groundbreaking therapies to thousands of patients around the world,” said Ger Brophy, general manager of cell therapy for GE Healthcare Life Sciences.

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At AACR 2018, Cellecta will be at Booth 2421.

Join us on Monday, April 16, 2018 from 10-11 a.m. for an educational workshop. AACR Exhibit Hall, Spotlight Theater C. McCormick Place, Chicago, Il. Genetic Profiling and Functional Screening for Drug Target and Biomarker Discovery

Sylvain Baron, Ph.D.
Research Scientist, Cellecta, Inc.

Lester Kobzik, M.D.
Professor of Pathology, Brigham & Women’s Hospital, Harvard Medical School, Harvard School of Public Health

Paul Diehl, Ph.D.
Chief Operating Officer, Cellecta, Inc.

Register for our workshop at www.cellecta.com/aacr2018

Who we are

Cellecta is a leading provider of genomic products and services. Our functional genomics portfolio includes gene knockout and knockdown screens, custom and genome-wide CRISPR and RNAi libraries, construct services, cell engineering, NGS kits and targeted expression profiling products and services.

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In the new biohybrid and medical textiles class, the biomaterials have been designed to ensure the quality and traceability of the preclinical research data. The biomaterials are first processed into textile structures using traditional textile techniques such as knitting, melting and electrospinning, then colonized by the cells using fibrous, which aids in functions such as blood coagulation. Once heart valves are produced, they are trained in a bioreactor for the natural blood flow and pressure occurring in the body before they are ready to be implanted.

Currently, the focus is on preclinical studies. However, the aim is to further test the results in clinical studies as well, which leads to challenges in data collection and analysis. "When you do research that is so close to clinical application, and everything is aimed at testing the results in human patients, you have to ensure the quality and traceability of the preclinical research data for all participants," comments Prof. Christian Apel, head of the Biohybrid and Medical Textiles department at the University. "Both the 'good scientific practice' and the regulatory authorities demand a complete record and safe storage of our research results. Of course, as a university institution, we also have many students and postgraduates who contribute a big deal to research.

BioCryst researchers have established that an ALK2 enzyme mutation is present in all cases of the ultra-rare disease FOP—or stone man disease—and the company is running two potential oral ALK2 inhibitor candidates through preclinical research with an eye toward human trials beginning next year. Isaac & Rose Nassau Professor of Orthopedic Molecular Medicine and co-director of The Center for Research in FOP & Related Disorders at the Perelman School of Medicine of the University of Pennsylvania. Kaplan and his colleagues at the University of Pennsylvania have clearly established that an activating mutation in the ALK2 (activin receptor-like kinase 2) gene is essential for disease-

**Double the good news**

BioLineRx’s BL-8040 and AGI-134 programs boost survival in preclinical studies

BY KELSEY KAUSTINEN

TEL AVIV, Israel—The first quarter of 2018 has been a positive one so far for biopharmaceutical company BioLineRx Ltd., which debuted encouraging data from two of its oncology programs at this year’s ASCO/SITC Clinical Immunology-Oncology Symposium. The symposium was held in late January in San Francisco. One of the featured candidates was BL-8040, BioLineRx’s lead oncology platform. The study found that BL-8040 boosts the immune system’s ability to fight cancer by increasing the flow of antitumor-specific T cells into the tumor microenvironment. Specifically, the poster abstract noted that the amount of antigen-specific CD8+ T cells in the microenvironment increased significantly. In a mouse model of cancer, this led to a drop in tumor growth and longer survival times: 35 days after tumor implantation, 80 percent of mice in the BL-8040 + vaccine group had survived, compared to none in the BL-8040 or vaccine treatment groups.

According to the presentation, the combination group consisted of BL-8040 administered along with “tumor-specific antigen priming using E7 peptide vaccine (three doses, one week apart),” a vaccine meant to “prime” the immune system against tumors. “I am highly encouraged by the data generated in this preclinical study, which further demonstrates the therapeutic potential of BL-8040,” said Dr. Samir Khleif, professor of oncology and director of the Loop Immunology-Oncology Laboratory at Georgetown Lombardi Comprehensive Cancer Center. “The results provide further evidence that BL-8040 promotes the infiltration of cytotoxic T cells into tumors, which is seen as a key objective to improve responsiveness to checkpoint therapy. I look forward to seeing the results from the clinical studies in which BL-8040 is being combined with other agents.”
BIOCRYST
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bioCryst's senior vice president and chief medical officer. “At bioCryst, we constantly strive to create medicines that not only treat serious rare diseases, but do so in a way that retains the best quality of life possible for patients and, ultimately, their families and caregivers as well.”

Dr. William P. Sheridan, chief medical officer of BioCryst looks normal on X-ray and under the microscope. It behaves like normal bone—if it bears weight, it gets denser, and if it doesn’t bear weight, it becomes osteoporotic. It’s normal in every way except one: it shouldn’t be there. “These people aren’t just forming little bones here and there. They are forming a whole extra skeleton. You never see the stomach turn into the small intestine. But here you see what seems to be perfectly normal muscle turn into perfectly normal bone. Normal bone.

“We are thrilled that our drug discovery culture has succeeded in bringing forward attractive oral ALK2 inhibitors that have the potential to treat patients with FOP. At BioCryst, we constantly strive to create medicines that not only treat serious rare diseases, but do so in a way that retains the best quality of life possible for patients and, ultimately, their families and caregivers as well.”

Dr. William P. Sheridan, chief medical officer of BioCryst said Dr. William P. Sheridan, BioCryst’s senior vice president and chief medical officer. “At BioCryst, we constantly strive to create medicines that not only treat serious rare diseases, but do so in a way that retains the best quality of life possible for patients and, ultimately, their families and caregivers as well.” Dr. William P. Sheridan, chief medical officer of BioCryst

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Dr. William P. Sheridan, chief medical officer of BioCryst looks normal on X-ray and under the microscope. It behaves like normal bone—if it bears weight, it gets denser, and if it doesn’t bear weight, it becomes osteoporotic. If you break it, it heals, just like a normal fracture. It even contains marrow. It’s normal in every way except one: it shouldn’t be there.”

But that may change thanks to the work of small-molecule researchers at BioCryst. They are exploring ALK2 inhibitors, with two potential lead candidates in nonclinical development. Preliminary results show promise for the possibility of the orally administered kinase inhibitor. The two lead candidate molecules dramatically reduced progressive formation of bone in soft tissues, also known as heterotropic ossification (HO), in laboratory rats, with up to 89-per-cent reduction in volume of HO compared to controls.

Tests indicate that the potential therapeutic is able to hit its target—it can be successfully absorbed into the blood and further absorbed into cells. The lead candidates for the inhibitor are currently being tested in accordance with regulatory requirements for proof of shape, potency, strength, exposure response and purity. Following testing on transgenic mice, the company expects to complete IND-enabling manufacturing and nonclinical safety studies to support Phase 1 trials beginning in 2019.

“We are thrilled that our drug discovery culture has succeeded in bringing forward attractive oral ALK2 inhibitors that have the potential to treat patients with FOP,” said Dr. William P. Sheridan, BioCryst’s senior vice president and chief medical officer. “At BioCryst, we constantly strive to create medicines that not only treat serious rare diseases, but do so in a way that retains the best quality of life possible for patients and, ultimately, their families and caregivers as well.”

So far, ALK2 is the only kinase known to be involved in FOP, both as a daily prophylactic to prevent HO growth, and as a short course to be taken following traumas that can cause a flare-up.

“With ALK2 being the only kinase involved in FOP, we are hopeful that a drug targeting ALK2 will be successful in treating FOP,” said Dr. William P. Sheridan, BioCryst’s senior vice president and chief medical officer. “At BioCryst, we constantly strive to create medicines that not only treat serious rare diseases, but do so in a way that retains the best quality of life possible for patients and, ultimately, their families and caregivers as well.”

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China- and U.S.-bound for RX-0201

Rexahn announces collaboration with Zhejiang Haichang Biotechnology for development of Archexin to treat hepatocellular carcinoma

BY DDNEWS STAFF

ROCKVILLE, Md. — In early February, Rexahn Pharmaceuticals Inc., a clinical-stage biopharmaceutical company developing targeted therapeutics for the treatment of cancer, announced that it had entered into a collaboration and license agreement with Zhejiang Haichang Biotechnology Co. Ltd. (Haichang) to develop RX-0201 (Archexin) for the treatment of hepatocellular carcinoma (HCC), the most common form of liver cancer.

Under the terms of the agreement, Haichang will develop a nano-liposomal formulation of RX-0201 using its proprietary QTsome technology and conduct certain preclinical and clinical activities through completion of a Phase 2a proof-of-concept clinical trial for the treatment of HCC.

“The incidence of liver cancer is growing worldwide, and especially in Asia,” said Daniel A. de Boer, CEO of ProQR. “We are impressed with Haichang’s QTsome technology. It has the potential to target RX-0201 to the liver and to promote uptake into cancer cells to enhance efficacy.”

“We are delighted to enter into this collaboration to take RX-0201 forward in hepatocellular carcinoma,” said Dr. Peter D. Suzdak, CEO of Rexahn. “We are impressed with Haichang’s QTsome technology. It has the potential to target RX-0201 to the liver and to promote uptake into cancer cells to enhance efficacy.”

“We are pleased with Haichang’s QTsome technology. It has the potential to target RX-0201 to the liver and to promote uptake into cancer cells to enhance efficacy.”

Dr. Stephen Rose, chief research officer for Foundation Fighting Blindness’ (FFB) retinal research program, adds Shah. “Therefore ProQR is very pleased to be part of this collaboration with FFB to advance this therapy for Usher syndrome patients.”

“FFB became aware of ProQR through the investigator FFB supported in the Netherlands, whose technology ProQR licensed,” notes Dr. Stephen Rose, Foundation Fighting Blindness’ chief research officer. “FFB initiated the research support that led to this technology. At ProQR, they have a very patient-centric approach to development and therefore work closely with patient organizations for the development of their programs.”

“We think our RUSH2A study results will be helpful for the simple reason that in order to determine if a treatment is effective, an endpoint that defines success in a clinical trial has to be determined. To do this, you have to know the clinical parameters of the disease onset and progression. The RUSH2A Natural History study will map the progression of Usher 2A retinal degeneration over time. Therefore, the clinical trial will be able to show if the treatment slows vision loss or even restores vision, as was seen in the RPE65/ LCA2 clinical trial that led to the December 2017 FDA approval of Spark Therapeutics’ LUXTURNA gene therapy.”

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BL-8040 is a short peptide being advanced as a treatment for solid tumors, acute myeloid leukemia, and stem cell mobilization. The compound is a high-affinity antagonist of CXCR4, a chemokine receptor that plays a role in tumor progression, angiogenesis, metastasis, and cell survival. This chemokine receptor is over-expressed in more than 70 percent of human cancers, with its expression commonly linked to disease severity.

As noted by BioLineRx, “In a number of clinical and preclinical studies, BL-8040 has shown robust mobilization of cancer cells and immune cells from the bone marrow, thereby sensitizing cancer cells to chemo- and bio-based anti-cancer therapy, as well as a direct anticancer effect by inducing cell death (apoptosis) and mobilizing immune cells. In addition, BL-8040 has also demonstrated robust stem cell mobilization, including the mobilization of colony-forming cells, T, B and NK cells.”

BioLineRx CEO Philip Serlin commented in a press release that the company is evaluating BL-8040 in eight ongoing clinical trials in multiple indications, ranging from solid tumors to blood cancers.

The other program highlighted in a poster presentation was AGI-134, an immunotherapy treatment being developed against multiple solid tumors. The presentation, “Intratumoral Administration of the Alpha-Gal Glycolipid AGI-134 to Induce Tumor Regression in a Mouse Model of Melanoma,” covered data from a pair of preclinical studies of AGI-134 in melanoma.

AGI-134, a synthetic alpha-Gal immunotherapy, is presently being developed against solid tumors. As noted by BioLineRx, “AGI-134 harnesses the body’s pre-existing, highly abundant anti-alpha-Gal antibodies to induce a systemic, specific antitumor response to the patient’s own tumor neoantigens. This response not only kills the tumor cells at the site of injection, but also brings about a durable, follow-on, anti-metastatic immune response.” The company has completed several preclinical studies of AGI-134, in which it has shown strong protection against the development of secondary tumors in a melanoma model after a single dose. AGI-134 also demonstrated some synergy when combined with a PD-1 immune checkpoint inhibitor.

The ASCO-SITC presentation looked at the results of AGI-134 in two mouse models: B16.F10 and B16.OVA. In the B16.F10 model, nearly 50 percent of AGI-134-treated tumors fully regressed, compared to 24 percent in the PBS controls. AGI-134 also improved survival, with only 23 percent of mice treated with AGI-134 dying or requiring euthanasia due to tumors by day 27 post-treatment, compared to 43 percent in the control groups. In addition, examining C5a levels two hours after treatment with either AGI-134 or PBS showed that the former triggered significant activation of the complement system in injected tumors. Such activation is believed to destroy tumor cells and encourage a pro-inflammatory tumor microenvironment that will attract and activate other immune cells, thereby leading to adaptive antitumor immunity. In the B16.OVA model, 67 percent of mice treated with AGI-134 saw their tumors fully regress vs. 0 percent in control mice in two assays.

Serlin said in a press release that “Previous studies have demonstrated that intratumoral administration of AGI-134 induces a systemic antitumor response that protects mice from the development of distant tumors. These new studies now show direct regression of established primary tumors after injection with AGI-134, and that this regression is associated with activation of the innate immune system. These compelling preclinical data support investigating this approach in a Phase 1/2a study, and we are excited and on track to commence a first-in-human study with this promising novel oncology asset in patients with solid tumors in the first half of 2018.”

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ever, they leave the institute after completing their project, which is not only a great pity, but also very frustrating to see data generated with great effort become irretrievable, hidden in paper notebooks or in unstructured or even inaccessible digital documents.

To tackle this challenge, RWTH researchers have opted for an electronic lab notebook (ELN) called labfolder from the eponymous company labfolder GMBH. Founded in 2013 by molecular biologist Simon Burgers (CEO) and biophysicist Florian Hauer (chief operating officer)—and joined later by Yannick Skop (chief commercial officer) and Mario Russo (chief technology officer), labfolder’s software-as-a-service (SaaS) makes it easier for researchers and supporting scientists to record, retrieve, share, discuss and validate research data as a team. To date, labfolder is used by more than 16,000 international scientists in all disciplines, as well as by industrial and pharmaceutical scientists in R&D, analysis and production labs.

The software streamlines utilities such as drag-and-drop data integration available on any computer or mobile device, access to Word and Excel documents and customizable entry forms. Teams are able to strategize and optimize their workflow, discuss and collaborate within the program and designate administrative controls. Additionally, labfolder can be integrated with apps such as Dropbox or the labfolder app itself, and is functional across all platforms and operating systems.

In terms of integrity and security, labfolder’s SaaS ELN software offers full version histories and time stamps, a sign-and-witness app and free daily backup to the cloud. Users retain all ownership of data loaded to the program, and nothing can be accessed unless it has been specifically shared to a team. In addition, labfolder meets all requirements for the fully compliant usage in GxP certified laboratories being compliant to the requirements for electronic recording according to both administrative controls. Additionally, labfolder can be integrated with apps such as Dropbox or the labfolder app itself, and is functional across all platforms and operating systems.

The decision by RWTH Aachen University to implement use of labfolder coincided with the opening of RWTH’s new Center for Biohybrid Medical Systems within the university’s biomedical engineering cluster earlier this year.

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The unique human Artificial Lymph Node model was developed by ProBioGen to be, as the company puts it, a “superior 3D-micro-organoid model for analyzing substance effects on the human immune system in vitro.”

Under the terms of the agreement, the technology platform will be transferred to TEVA as a predictive tool to assist in the assessment of TEVA’s bio-pharmaceutical drug candidates.

“A deal for artificial lymph node technology

ProBioGen and TEVA enter into research license deal on tech to assess drug effects on the immune system

BY DDNEWS STAFF

BERLIN—ProBioGen, a specialist for contract development and manufacturing of complex glycoproteins, announced in February the signing of a non-exclusive license agreement on its proprietary human Artificial Lymph Node (HuALN) platform technology with TEVA. The unique human Artificial Lymph Node model was developed by ProBioGen to be, as the company puts it, a “superior 3D-micro-organoid model for analyzing substance effects on the human immune system in vitro.”

Under the terms of the agreement, the technology platform will be transferred to TEVA as a predictive tool to assist in the assessment of TEVA’s bio-pharmaceutical drug candidates.

“With the complex, in-vivo-like human Artificial Lymph Node model we have demonstrated effects which were impossible to see in conventional models, bridging the existing gap between animal models and first-in-man applications,” says ProBioGen’s chief scientific officer Dr. Volker Sandig. “We look forward to this collaboration and the combined expertise on either side to develop the HuALN platform even further.”

HuALN was developed by ProBioGen and is based on a patented, miniaturized and perfused bioreactor for long-term cultivation of immune cells. Human blood-derived dendritic cells, T and B lymphocytes and mesenchymal stem cell-derived stromal cells are inoculated into the bioreactor’s three-dimensional hydrogel matrix, which is perfused with cell culture medium and seeded just as in a real human lymph node, according to ProBioGen. Upon antigen-stimulation, the cells self-organize into immune-competent micro-organoid structures within the 3D matrix. The perfused bioreactor is typically operated for four weeks, and thus allows multiple and repeated examinations of the immune cells to the test compounds.”
**VIRAL SUPPRESSION**

Study investigates two new drugs for HIV

*BY ILENE SCHNEIDER*

BRENTFORD, U.K.—There are about 34 million people living with HIV/AIDS across the world, and HIV treatment is a continuing and persistent effort. Currently, a stabilized patient receives three drugs daily, but an effort is being made to see if this can be reduced to two.

According to GlaxoSmithKline (GSK), the two new drugs are lamivudine, a nucleoside analog given the brand name Epivir, and dolutegravir, an integrase strand transfer inhibitor (INSTI) that will be marketed as Tivicay. An INSTI stops HIV virus production by keeping the viral DNA from entering the nucleus of the patient’s T cells. Lamivudine is available in branded and generic forms, and Tivicay is approved in over 100 countries across North America, Europe, Asia, Australia, Africa and Latin America.

Both drugs were created by ViV Health-care, a company founded in 2009 by Vivekananda R paste MABp1, respectively.

**Clinical trial for solid tumor combination treatment**

MARSEILLE, France—A clinical trial collaboration is now underway between Innate Pharma SA and MedImmune, the global biologics research and development arm of AstraZeneca. Under the auspices of the deal, the companies will assess the safety and efficacy of durvalumab, an anti-PD-L1 immune checkpoint inhibitor, in a Phase 1/2 study of individuals with select solid tumors. The compound will be tested in combination with Innate’s True Human antibody MABp1 as a treatment for hidradenitis suppurativa. The study’s primary endpoint was reached, with significant treatment benefit seen using the HSICR endpoint.

**Replacing a needle with a pill**

Allergan achieves positive top-line Phase 3 results for oral CGRP receptor antagonist targeting acute treatment of migraine

*BY LORI LESKO*

DUBLIN—Aimed at relieving and preventing the debilitating effects of migraine without the adverse effects of opioids, global pharmaceutical Allergan plc has come up with its first oral calcitonin gene-related peptide (CGRP) receptor agent in the form of a pill, as opposed to an injection.

On Feb. 6, Allergan announced positive results from ACHIEVE I (UBR-MD-01), the first of two pivotal Phase 3 clinical trials evaluating the efficacy, safety and tolerability of orally administered ubrogepant (50 mg and 100 mg compared to placebo) in a single migraine attack in adults.

The study met co-primary endpoints in the first of two Phase 3 studies.

Considered potential game-changers, Allergan’s CGRP receptor antagonists—ubrogepant in Phase 3 for the acute treatment of migraine and atogepant in Phase 2B for the prevention of migraine—are expected to be considered potential game-changers, Allergan’s CGRP receptor antagonists—ubrogepant in Phase 3 for the acute treatment of migraine and atogepant in Phase 2B for the prevention of migraine—are expected to be

**A digital path for studies**

TriNetX tech helps Sanofi streamline clinical trial protocols, improve efficiency and extend digital strategy

*BY MEL J. YEATES*

PARIS & CAMBRIDGE, Mass.—Researchers have come to increasingly rely on computer technology to make their work more productive. Nowhere is that more relevant than in biopharmaceuticals, where Sanofi has used advanced digital technology as one of its key strategies. One of the major areas of focus for the company is to improve the clinical trial process, in order to reduce drug development cycle times and costs.

Sanofi announced in January a collaboration with TriNetX, a health technology and data company which operates an extensive cloud-accessible federated health research platform. TriNetX technology can be applied to clinical trials in a variety of ways that promise to reduce the complexity of trial design, increase recruitment success and help streamline the work of trial investigators.

Jennifer Haas, vice president of marketing at TriNetX, tells DDNews, “Sanofi has been one of the early adopters of the TriNetX platform, dating back to 2016. Sanofi leverages TriNetX for protocol design, patient feasibility analysis and site selection. A more strategic partnership evolved over the course of business.”

“Clinical trials are the essential link between our laboratory research and the real-world proof of effectiveness and safety that we need to provide to regulators in order to bring innovative therapies to the patients who need them,” said Lionel Bascales, global head of clinical sciences and operations for Sanofi. “Clinical trials are becoming ever more complex, and anything we can do to reduce the time and cost of clinical trials is crucial.”
A roundup of clinical trial startups and initial breakthroughs

BY JEFFREY BOULEY
LEXINGTON, Mass.—In a tour of recent trial phase starts and early work in various phases, let’s begin with Concert Pharmaceuticals Inc., which in mid-February announced that it had initiated enrollment of the second cohort of its Phase 2a clinical trial evaluating CTP-543. Concert is developing CTP-543 for the treatment of moderate-to-severe alopecia areata, an autoimmune disorder in which the immune system attacks hair follicles, resulting in patchy or complete hair loss. CTP-543 is a deuteron-modified analog of ruxolitinib, a Janus kinase (JAK) inhibitor.

An independent data monitoring committee conducted an interim safety data review of the first cohort of the Phase 2a trial, following 12 weeks of dosing with a mg of CTP-543 or placebo twice daily. Based on this review, the DMC provided its recommendation to continue with the current cohort and to initiate dosing of the second cohort, whereby patients will be administered 8 mg of CTP-543 or placebo twice daily for 24 weeks. The company expects to report top-line data from the Phase 2a trial in the fourth quarter of this year.

“We are pleased that the CTP-543 trial is progressing as planned as we continue to advance the evaluation of our innovative product candidate for alopecia areata,” said Dr. James Casella, chief development officer of Concert Pharmaceuticals. “There is a significant unmet medical need for alopecia areata, and we intend to be at the forefront of advancing a new oral treatment for patients.”

The Phase 2a trial is a double-blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of CTP-543 in adults with moderate-to-severe alopecia areata. Approximately 90 patients are being enrolled in the study and randomized to receive one of two doses of CTP-543 (4 mg or 8 mg) or placebo twice daily. The primary outcome measure will utilize the severity of alopecia tool (SALT) after 24 weeks of dosing. Patient-reported outcome measures will be assessed as secondary endpoints. If appropriate, the protocol may be amended to explore higher doses of CTP-543.

**Applied Therapeutics begins trial for AT-001 in diabetic complications**

NEW YORK—The same day as the Concert Pharmaceuticals news, Applied Therapeutics Inc., a privately held biotechnology company focused on developing transformative drugs in areas of high unmet medical need, announced initiation of a Phase I clinical trial for AT-001, an oral small molecule in development for diabetic complications.

The Phase I clinical trial is a first-in-human, randomized, placebo-controlled, dose escalation study to assess the safety and tolerability, pharmacokinetics and pharmacodynamics of AT-001 in patients with type 2 diabetes. The study will also evaluate a specific biomarker to assess patient response.

“Initiation of this study represents a significant milestone for Applied Therapeutics as we advance our first compound, AT-001, into the clinic,” commented Dr. Shoshana Shendelman, founder, chairman and CEO of Applied Therapeutics.

**Allergan believes oral therapy—as opposed to injection—will appeal to individuals with migraine, and is exploring a couple different oral agents now: one for acute treatment of migraine and another for prevention.**

Allergan believes oral therapy, as opposed to injection, will appeal to individuals with migraine. Migraine is defined as a chronic disease with episodic attacks characterized by neurological symptoms—such as headache pain, nausea and sensitivity to light and sound—that are often incapacitating.

The current standards of care in the acute treatment of migraine are not optimal for many patients due to partial effectiveness, poor tolerability or contraindications, Nicholson says. As a consequence, patients may experience repeated, uncontrolled attacks leading to medication overuse, possible opioid addiction and increased risk of migraine disease progression.

Chronic migraine is a distinct neurological condition affecting 3.2 million Americans, defined as having 15 or more headache days per month, with headaches lasting four hours a day or longer and at least eight of those headache days being associated with migraine, Nicholson explains. One of seven adults suffer from migraine episodes globally.

Ubrogepant is a novel, highly potent, orally administered CGRP receptor antagonist in development for the acute treatment of migraine, Nicholson says. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology. CGRP receptor antagonism is a novel mechanism of action for the acute treatment of migraine that clearly differs from the mechanisms of currently available triptans (serotonin 1B/1D agonists) and opioids.

Allergan has marketed Botox, an injection therapy, but believes more people would take advantage of a new migraine therapy in pill form, Nicholson notes. Botox is the first and only FDA-approved (in 2010) preventive treatment for chronic migraine. According to Allergan, unlike acute treatments, which are taken to treat a headache or migraine once it’s already begun, Botox prevents headaches and migraines before they even start. Botox prevents on average eight to nine headache days and migraine/probable migraine days a month (vs. six to seven for placebo).

The ACHIEVE I study included 1,327 U.S. adult patients randomized to placebo, ubrogepant 50 mg or ubrogepant 100 mg, who were treated for a single migraine attack of moderate to severe headache intensity. Both doses showed a statistically significant greater percentage of ubrogepant patients achieving pain freedom at two hours after the initial dose as compared to placebo patients. The study also found that ubrogepant was well tolerated, with an adverse event profile similar to placebo. The most common adverse events were nausea, somnolence and dry mouth—none of which were reported with a frequency of more than 5 percent.

In terms of hepatic safety, across all treatment arms including placebo, there were six cases with aminotransferase (ALT or AST) elevations greater than three times the upper limit of normal. There were alternative explanations in all cases (concomitant illness or medication), and none were noted by the liver safety adjudication board to have a probable relationship to ubrogepant. Also, there were no cases of Hy’s Law, which states that hepatocellular drug-induced liver injury with jaundice indicates a serious reaction and is used widely to determine risk for acute liver failure.

“Despite the prevalence of migraine and availability of several treatment options, the disease remains underdiagnosed and undertreated,” states lead investigator Dr. Richard B. Lipton, vice chair of neurology, professor of epidemiology and population health and director of the Montefiore Headache Center at the Albert Einstein College of Medicine. “There is also low persistence and adherence to the current standard-of-care treatments. There remains a need for new treatments with improved benefit-risk profiles. Results from this ubrogepant Phase 3 trial are important in progressing the research and developing therapies to help migraine patients.”

Additional results from this Phase 3 study are anticipated to be released at upcoming scientific meetings throughout 2018. Results of the second Phase 3 trial, ACHIEVE II (UBR-002), are expected in the first half of 2018. Allergan anticipates filing of a New Drug Application to the FDA in 2019.
ViiV

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Pharma giants GlaxoSmithKline and Pfizer, joined by Shionogi Ltd. in 2012. The companies got together following a long-term collaboration on the joint development of several novel integrase inhibitors.

ViiV Healthcare regards its mission in beating the disease as dedicating itself to providing advances in treatment and care for people living with HIV. According to the company website, “ViiV Healthcare is 100 percent dedicated to HIV medicines and research and completely focused on people affected by HIV/AIDS. Scientists are 100 percent dedicated to finding new ways to limit the impact of HIV on the people living with the virus and understanding how best to prevent and treat the disease.”

As Dr. John C Pottage Jr., chief scientific and medical officer of ViiV Healthcare, explained, “We are asking a simple question in the TANGO study—can virally suppressed people with HIV reduce the number of medicines in their HIV treatment regimen while maintaining viral suppression? If the data show the answer to be yes, this may allow healthcare providers to address issues of long-term toxicity by reducing exposure to antiviral agents over a lifetime of treatment. We believe that with its high barrier to resistance, dolutegravir has the right clinical profile to be a core part of 2drug [two-drug regimen] for the treatment of HIV-1, and look forward to seeing the results of TANGO in 2019.”

TANGO refers to the Phase 3 randomized, parallel group clinical trial now underway with 550 HIV patients, which will compare the new drugs’ performance with the existing three-drug treatment for 96 weeks. TANGO will attempt to enroll about 550 adults with HIV-1, from clinical trial sites in North America, Europe, Australia and Japan. If the new drug proves superior, patients receiving the current therapy will be switched over in 48 weeks.

The TANGO study follows the GEMINI studies’ investigation of the 2DR of dolutegravir and lamivudine in treatment-naive patients with HIV-1. Results from those trials are anticipated later this year.

ViiV’s current portfolio of 12 HIV treatments accounted for annual sales of £2.3 billion in 2015, giving the company the financial stability to “take a sustainable, long-term view when investing in our pipeline of new medicines.” The staff of more than 700 people works in 15 countries. The company extends its geographical reach even further because of its relationship with GSK to establish a presence in more than 65 countries around the world. ViiV maintains it is equipped to move quickly in response to the needs of the HIV community and has launched numerous access initiatives to help deliver on World Health Organization/UNAIDS goals to reach all those who need treatment.

The staff of more than 700 people works around the world. ViiV main-
Continued from page 35

Clinical trials begin with the creation of a protocol—a complete description of the study, its objectives, patient profiles based on medical characteristics, milestones and patient outcomes. That alone is a complex undertaking that companies like Sanofi want to streamline. Frequently, there is a need to amend the protocol during the trial for any number of reasons, and the more amendments there are (and the more complex), the more time the trial will take—and the more it will cost.

Sanofi has turned extensively to the application of digital technology and analysis, both its own and from outside partners, to address many of these problems. Notes Haas, “Sanofi, as do most pharmaceutical companies, sits on lots of data; being able to leverage that intelligence in combination with external data partners presents opportunities to accelerate clinical research.”

“The hallmark of TriNetX is a real-world evidence-based platform that presents data through a user-friendly application with rich analytics, rendering it applicable in the designing of protocols, assessing of feasibility and identification of a potential patient cohort,” Haas explains. “The TriNetX data set is a unique asset and analysis tool, significantly reducing the time (to a matter of minutes)—what traditionally has taken weeks or months to perform, can now be done in real-time by trial investigators.”

TriNetX’s technology can analyze billions of clinical facts about its patient population to support real-time modeling of proposed clinical trial protocols. Researchers can quickly visualize how these protocols would be expected to operate in an actual trial and make rapid modifications to accommodate that information. The technology also uses predictive analytics, so researchers can forecast the expected size of the patient population that might meet the study criteria.

The technology provides access to investigators and institutions who not only can help carry out the trial, but also are most likely to help identify eligible patients for the trial who otherwise might be missed.

TriNetX’s global health research network consists of 68 healthcare organizations, representing 95 million patients. TriNetX combines electronic medical record data with genomics and deep oncology data, then presents that data through a user-friendly application that enables pharmaceutical companies to analyze patient populations and perform “what-if” analyses in real time,” says Haas. “Biopharmaceutical companies and clinical research organizations have access to the institution’s de-identified patient data and are presented with aggregate views, but each data point in the TriNetX network can be traced to healthcare organizations who have the ability to identify individual patients, allowing clinical researchers to develop virtual patient cohorts that can then be re-identified for potential recruitment into a clinical trial.”

“The application of real-world evidence combined with advanced analytics takes the ambiguity out of clinical trial design, and we are very proud of the contributions that our technology has had on Sanofi’s efforts to reduce amendments and improve trial efficiency,” said Gadi Lachman, CEO of TriNetX. “Working with Sanofi and its extensive set of ongoing and planned clinical trials also brings significant value to TriNetX’s healthcare organization members, both in the U.S. and globally.”

TriNetX joins two other key relationships Sanofi has established in digital clinical trials in the past year. In March 2017, Sanofi announced a working relationship and investment in Science 37, a Los Angeles-based company that facilitates and oversees digital clinical trials, making it possible to work readily with a widely dispersed patient population and gather real-time data on the trial. In July 2017, Sanofi also announced a relationship with Evidation, which identifies and monitors digital biomarkers in patients to better understand therapeutic outcomes and the different factors that may affect those outcomes.

“Sanofi is proud to be working with leading companies around the world to implement our digital strategy in an effort to bring great drugs to the right patients, faster,” remarked Heather Bell, global head of digital and analytics at Sanofi. “We are delighted to welcome TriNetX to our group of digital partners; our new collaboration is an important step in Sanofi’s systematic effort to digitize clinical trials.”

“Clinical trials are becoming ever more complex, and anything we can do to reduce the time and cost of a trial means therapies can be evaluated more rapidly and reach people faster,” says Lionel Bascles, global head of clinical sciences and operations for Sanofi. "Working with companies like TriNetX is an important way to do that, by bringing both technology and knowledge to Sanofi’s work.”

Sanofi has been one of the early adopters of the TriNetX platform, dating back to 2016,” says Jennifer Haas, vice president of marketing at TriNetX. “Sanofi leverages TriNetX for protocol design, patient feasibility analysis and site selection. A more strategic partnership evolved over the course of business.”

Sanofi, as do most pharmaceutical companies, sits on lots of data; being able to leverage that intelligence in combination with external data partners presents opportunities to accelerate clinical research.”

Jennifer Haas, vice president of marketing at TriNetX
Acesion Pharma gets nod for Phase 1 study in atrial fibrillation

COPENHAGEN, Denmark— Early February saw Acesion Pharma, a Danish biotech company developing novel treatments for atrial fibrillation (AF), the most common cardiac arrhythmia, announce that it had received approval to commence its first clinical study for its lead compound AP06665. The Phase 1 study in healthy subjects will be conducted at the Centre for Human Drug Research (CHDR) in the Netherlands and was due to start this month.

The incidence of AF increases with age, and it is estimated that 5 to 10 percent of the population above the age of 70 have AF. It is a progressive disease that is associated with significant morbidity and a fivefold increased risk of stroke. Existing drug therapies for AF, using other modes of action, have encountered major safety issues due to their effects on the ventricles, leading to life-threatening pro-arrhythmia and/or depression of the myocardial function. In addition, their efficacy and/or tolerability has limited their use and there remains a significant need for developing better, safer and more tolerable treatments.

Acesion is developing a portfolio of drugs addressing both acute and persistent AF. Acesion’s novel approach is based on inhibition of SK channels—ion channels present in the atria that play a role in regulating the cardiac rhythm. Blocking these ion channels with a functionally atrial-selective drug helps avoid deleterious effects on the ventricles. Targeting the SK channels thereby constitutes a novel and promising approach for an effective treatment of AF with an expected higher safety and tolerability profile.

Second ZX008 Phase 3 trial in Dravet syndrome

EMERYVILLE, Calif.—Stepping back just a bit to late January, Zogenix Inc., a pharmaceutical company developing therapies for the treatment of rare central nervous system (CNS) disorders, announced that the last patient has been randomized into the treatment period of Study 1504, its second Phase 3 clinical trial evaluating ZX008 (low-dose fenfluramine) as an adjunctive treatment for seizures in children and young adults with Dravet syndrome.

Previously, in the third quarter of 2017, the company announced positive top-line data from its first global Phase 3 trial of ZX008, Study 1, that met the primary efficacy endpoint and all prespecified key secondary efficacy endpoints.

“The completion of patient randomization in Study 1504 represents another significant achievement in our ZX008 Phase 3 development program in Dravet syndrome,” said Dr. Stephen J. Farr, president and CEO of Zogenix. “We expect to announce top-line data from this study in the second quarter of this year. The data generated to date from the Phase 3 clinical program have further strengthened our confidence in the potential of ZX008 to become an important treatment option for the control of seizures in patients suffering from Dravet syndrome, a rare and catastrophic form of epilepsy.”

ZX008 is designated as an orphan drug in both the United States and Europe, and has received Fast Track designation in the United States for the treatment of Dravet syndrome.

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A quick look at some recent cutting-edge work in the neuroscience arena

BY JEFFREY BOULEY

F NEXT MONTH’S Special Report on Neuroscience is the gourmet meal with a particular culinary focus, consider this month’s special focus section the sampler platter of various world cuisines. And first on that menu, we wanted to cover some slightly off-the-beaten-path topics that recently made the news rounds, beginning with what could be considered irony or synergy depending on your point of view: Artificial intelligence being put to work on human neurological concerns.

Specifically, BullFrog AI Inc., which focuses on artificial intelligence and clinical data analytics services, and the Lieber Institute for Brain Development, an independent, not-for-profit medical research institute working to accelerate efforts to find new cures for developmental brain disorders, recently announced a joint collaboration to apply BullFrog AI’s proprietary artificial intelligence platform to analyze antipsychotic drug responses.

Choosing and dosing antipsychotic drugs represents one of the most challenging areas for clinicians and patients alike, the partners note, with patients experiencing wildly differing responses to the different drugs on the market, particularly when it comes to the side effects: “The selection of the best drug for the particular patient then becomes a matter of educated guesswork, potentially causing distress and even harm to patients and those around them.”

To help turn the tide on that, BullFrog AI will utilize its proprietary artificial intelligence platform to analyze large multifactorial clinical data sets from patients who received antipsychotic medication, with an eye toward making it possible to better predict which patients respond best to which medications. “We are excited to partner with BullFrog AI on this challenging clinical problem,” said Dr. Kristin Bigos, an investigator at the Lieber Institute for Brain Development. “Until now there has been no effective alternative to the trial-and-error approach for matching patients to the best antipsychotic. Being able to understand and predict a priori which drugs will work best for which patients would be of tremendous benefit to both patients and the physicians that serve them.”

The bfLEAP analytics engine is purpose-built for analyzing extremely large and complex data sets, and it reportedly has demonstrated 99.9-percent accuracy in predicting the right targets across multiple data sets. The key to its success is the artificial learning, which requires no domain expertise, BullFrog AI maintains—instead, it uses unsupervised machine learning coupled with the world’s largest collection of analytical models, all operating in parallel.

And it’s not just clinical treatment with approved drugs where this effort could help, but also potentially in clinical trials. “bfLEAP represents a true leap forward in terms of our ability to understand what is going on in a complex clinical setting,” said Vin Singh, CEO of BullFrog AI. “For the first time, we are able to analyze massive, multifactorial clinical datasets and determine the root cause of the observed clinical outcomes. Using our platform, we can examine clinical trial data and identify relationships between patient-specific factors and clinical response, which may aid in predicting clinical trial outcomes in the future. The potential impact of this type of information for the pharmaceutical industry is enormous, both in terms of the reduced cost and increased revenue from failed drugs as well as the positive impact on patients.”

New insight on potential neurological cell therapies

COMING NEXT MONTH:

Special Report on Neuroscience

Plant extracts have long served as sources of new medicines, and to this day, serve as the basis of folk remedies such as traditional Chinese medicine. Even within the Western world, however, there is growing interest in the medicinal opportunities afforded by one plant in particular—Cannabis—particularly as it has been made legal in several U.S. states and is set to be legalized across Canada this summer.

With this interest in mind, the April 2018 DDNews Special Report on Neuroscience by Randall Ullman will examine recent efforts to understand the therapeutic potential of compounds found within Cannabis species, and in particular, their impact on neurological conditions such as epilepsy, amyotrophic lateral sclerosis, Parkinson’s disease and autism spectrum disorder.

The use of machine learning may put an artificial intelligence platform in a position to predict who will respond to various antipsychotic drugs, which could help not just clinical care but also clinical trial design for evaluating experimental drugs and testing for new indications of approved drugs.
LA JOLLA, Calif.—The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has awarded scientists at The Scripps Research Institute (TSRI) a $10-million grant to study how long-term alcohol use changes basic mechanisms of brain function. The researchers will then investigate how novel medications derived from this work may reverse those changes to treat alcohol addiction.

The five-year grant will support five individual research projects and three core resources at the TSRI Alcohol Research Center (TSRI-ARC), and will be led by Dr. Barbara Mason, the Pearson Family Chair and center director of TSRI-ARC. Together, the projects—involving molecular pharmacology, neurochemistry, electrophysiology, neurocircuitry and clinical studies—aim to better understand what happens in the brain during the extended withdrawal phase a person goes through when they stop drinking, and to develop ways to treat that phase and prevent relapse.

"After someone with alcohol use disorder stops drinking and undergoes acute withdrawal, there’s then a protracted withdrawal phase that’s characterized by activation of stress systems in the brain and symptoms of negative affect such as anxiety, dysphoria and irritability," says Mason. “These symptoms ultimately drive craving and relapse, and we want to stop that cycle."

Around 80 percent of those who seek treatment for their alcohol use will relapse within a year. Animal models have hinted that reversing some of the changes in the brain caused by long-term alcohol use can prevent relapse. Mason and her colleagues want to probe that observation in more molecular detail and help translate it to humans.

“There hasn’t been a new pharmacological treatment for alcohol dependence in decades," says Mason. “We want to change that and help facilitate a return to homeostasis in the brains of people with alcohol use disorder.”

Mason’s research has already revealed that when someone with alcohol use disorder stops drinking, their brain releases stress neuropeptides—molecules that turn on stress pathways in the brain. They’ve also homed in on the extended amygdala—an area of the brain involved in mediating emotional behaviors—as helping mediate the interactions between stress and addiction.

Resources at TSRI-ARC are available to not only TSRI scientists, but researchers throughout the region. The new grant includes funds to help facilitate outreach to the community about alcohol use disorder. Scientists will share their results as well as information on addiction resources through lectures and events at high schools, senior citizen centers and other public venues.

Dr. Barbara Mason, the Pearson Family Chair and center director of TSRI-ARC.

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process to maintain their population, as well as differentiate to give rise to all neural cell types: neurons, astrocytes, and oligodendrocytes.

The SBP study focused on the self-renewal aspect of NSCs. Using knockout mice for the enzyme that catalyzes the m6A modification, Zhao’s team found that m6A modification maintains NSC pool by promoting proliferation and preventing premature differentiation of NSCs. Importantly, the researchers found that m6A modification regulates this by regulating histone modifications.

The importance of this lies in the fact that histones play an important part of turning genes on or off—these proteins bind and package DNA to “hide” a gene from the cell’s protein-making machinery (off) or “loosen up” DNA for gene expression (on).

Our findings are the first to illustrate cross-talk between mRNA and histone modifications, and may lead to new ways to target genes in the brain, says Zhao. “Conceptually, we could use the modification, which is the methyltransfer of adenosine residues, as a ‘code’ in mRNA to target histone modifications to turn genes on or off.

As SBP notes, drugs that can alter histones are far from a new concept in psychiatric and neurological care—“the problem is they are often not very specific and affect the entire genome.”

“Our current study addressed the interaction between mRNA and histone modification in a genome-wide scale. In the future, we plan to study such interaction on a gene-by-gene basis. Ultimately, by modulating mRNA modification and its interacting histone modifications at a specific genomic region, we hope to correct aberrant gene expression in brain disorders with precision,” explains Zhao.

“Tapping down Tourette disorder”

Finally, looking at an underserved area of neurological therapy, Therapix Biosciences Ltd., a specialty clinical-stage pharmaceutical company focusing on the development of cannabinoid-based treatments, announced early in February that it has held a pre-Investigational New Drug (pre-IND) communication with the U.S. Food and Drug Administration (FDA) to discuss the regulatory pathway for the development of THX-110 for the treatment of Tourette syndrome.

“Following this informative communication with the FDA, we can confirm that the IND for THX-110 will not require any additional nonclinical data to support a Phase 2b study in the United States. We intend to submit the NDA via the 505(b)(2) pathway. We believe that this enables us to continue our clinical program with minimum risk, which is consistent with our platform’s focus on targeting mRNA and histone modification in a genome-wide scale,” said Dr. Ascher Shmulewitz, chairman and interim CEO of Therapix. “If approved, THX-110 could provide people who suffer from Tourette syndrome with a treatment alternative to the anti-psychotic agents.”

THX-110 is a combination drug candidate for the treatment of Tourette syndrome and obstructive sleep apnea that is based on two components: dronabinol (an FDA-approved synthetic analog of Δ9-tetrahydrocannabinol (THC, which is the psychoactive molecule in the cannabis plant) and palmitoylethanolamide (PEA), an endogenous fatty acid amide that belongs to the class of nuclear factor-κB agonists, which are proteins that regulate the expression of genes). The combination of THC and PEA may induce a reaction known as the “entourage effect.”

The basic tenet of the entourage effect is that cannabinoids work together, or possess synergy, and affect the body in a mechanism similar to the body’s own endocannabinoid system, which is a group of molecules and receptors in the brain that mediates the psychoactive effects of cannabis.

PEA may indirectly stimulate the cannabinoids by potentiating their affinity for a receptor or by inhibiting their metabolic degradation, and by doing so, may increase the concentration of agonist compounds, such as THC. Thus, it is speculated that the presence of the PEA molecule could increase the efficacy of orally administered THC, while reducing the required dosage and decreasing associated deleterious adverse events.

Tourette syndrome is a neuro-psychiatric disorder characterized by physical and vocal tics—sudden, brief, intermittent, involuntary or semi-voluntary movements or sounds, respectively. The severity of the disorder can vary widely, from mild symptoms that do not cause serious impairment and are often go unnoticed, to loud noises and forceful movements that can result in self-injury. Many with the condition experience additional neurobehavioral problems and conditions, including learning disabilities, obsessive-compulsive disorder and attention deficit-hyperactivity disorder.

Dr. Jing Crystal Zhao, an assistant professor at Sanford Burnham Prebys Medical Discovery Institute.

“New understanding of an mRNA modification holds promise for better application of stem cell therapies for neurological conditions, according to researchers at the Sanford Burnham Prebys Medical Discovery Institute.”

Relmada acquires rights to dextromethadone for nervous system disorders treatment

NEW YORK—Relmada Therapeutics Inc., a clinical-stage company developing novel therapies for the treatment of central nervous system (CNS) diseases, recently acquired the global rights to develop and market dextromethadone (REL-1017), a novel N-methyl-D-aspartate (NMDA) receptor antagonist, for the treatment of neurological conditions including certain rare diseases with symptoms affecting CNS.

The company expects to select and initiate development for additional indications in 2018. Relmada previously acquired the global rights to dextromethadone for the treatment of symptoms associated with a range of psychological and psychiatric disorders including depression, anxiety, fatigue and mood instability, and it plans to start to enroll patients in a Phase 2a randomized, double-blind, placebo-controlled study of two dose levels of dextromethadone as a rapidly acting adjunctive treatment in patients affected by major depression in the first half of 2018.

“The clinically proven mechanism of action of dextromethadone shows potential benefits in the treatment of a wide range of CNS diseases and conditions, including rare diseases that represent significant areas of unmet need in healthcare,” said Sergio Traversa, who serves as the CEO of Relmada Therapeutics. “We believe that this new agreement is the most important transaction for Relmada since its inception, positioning us to target a wide range of development and global marketing opportunities for dextromethadone in the years ahead.”

The NMDA receptor is a therapeutic drug target for many CNS disorders and is a predominant molecular device for controlling synaptic plasticity and memory function, allowing for the transfer of electro-chemical signals between neurons. Based on this clinically proven mechanism of action, several NMDA receptor antagonists, including dextromethadone, are considered as therapeutic agents for CNS disorders.

In April 2017, Relmada announced that the U.S. Food and Drug Administration had granted Fast Track designation for dextromethadone for the adjunctive treatment of major depressive disorder.

The company plans to advance the development program of dextromethadone to a Phase 2a randomized, double-blind, placebo-controlled study that will assess changes in depressive symptoms as well as the safety, tolerability and pharmacokinetics of two dose levels of dextromethadone as a rapidly acting adjunctive treatment in patients affected by major depression. The company has also initiated a preclinical program to identify the most appropriate additional neurological indications for dextromethadone, including certain rare syndromes affecting the CNS.

Relmada is currently developing dextromethadone as a rapidly acting agent for the treatment of depression. Working through the same brain mechanisms as ketamine, a non-competitive NMDA channel antagonist, but potentially lacking its adverse side effects, dextromethadone is fundamentally differentiated from all currently FDA-approved antidepressants, as well as all atypical antipsychotics used additively.

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

EDITCONNECT: E031842
How the brain turns chronic stress into pathological anxiety

LA JOLLA, Calif.—In a new study, researchers at The Scripps Research Institute (TSRI) have described how two important molecules in the brain work together to trigger intense anxiety.

The new findings in animal models point to a novel interaction in the regulation of the brain’s stress response that may underlie the pathological anxiety related to symptoms of post-traumatic stress disorder (PTSD).

“Anxiety and stress disorders affect millions of people worldwide,” explained study leader Marisa Roberto, a professor at TSRI. “Understanding the mechanisms underlying these disorders is important for identifying potential new targets for therapeutic use.”

The researchers focused on the endogenous cannabinoid (endocannabinoid or eCB) system, which include natural lipid signaling molecules that bind to cannabinoi receptors in the brain. Cannabinoid (type 1) receptors control stress-mediating circuits by inhibiting neurotransmitter release—a sort of gating mechanism to keep anxiety in check.

In contrast to the stress-reducing proper-
“Anxiety and stress disorders affect millions of people worldwide. Understanding the mechanisms underlying these disorders is important for identifying potential new targets for therapeutic use.” Marisa Roberto, a TSRI professor

ties of endocannabinoids, a peptide molecule called corticotropin-releasing factor (CRF) activates the stress response and promotes increased sensitivity to stress and anxiety when activated over and over again.

In the new study, titled “Constitu-
tive increases in amygdalar corticotro-
pin releasing factor and fatty acid amide hydrolase drive an anxious phenotype” and published in the journal Biological Psychiatry, the researchers investigated the interaction between the stress-promoting (CRF) and stress-constraining (eCBs) mechanisms in the central nucleus of the amygdala, a critical brain region involved in mediating emotional reactions.

The findings suggest that overactive CRF signaling in this region produces a wide range of effects that override the stress-reducing capabilities of a major eCB called N-arachidonylethanolamine (anandamide), turning chronic stress into unchecked, or pathological, anxiety.

“Anxiety is something that everyone experiences on a day-to-day basis,” said study first author Luis A. Natividad, a research associate at the Roberto lab. “But it is unclear what changes this otherwise natural process into something debilitating.”

To answer this question, Roberto’s lab teamed up with Roberto Ciccocioppo’s lab at the University of Camerino in Italy and the lab of TSRI professor Loren (“Larry”) Parsons, a renowned leader in the fields of endocannabinoid signaling, stress and drug addiction who passed away in 2016.

The researchers studied rats that were genetically selected for higher alcohol drinking and also display an anxiety-like phenotype. These rats exhibit a mutation in a gene called Crhr1 that increases CRF (type 1) receptor signaling.

Using behavioral, neurochemical and electrophysiological approaches, the researchers found that increased CRF signaling led to elevated activity of the anandamide clearance enzyme fatty acid amide hydrolase (FAAH). Increased CRF was also associated with drops in anandamide levels in the central nucleus of the amygdala. Together, increased FAAH activity and decreased anandamide signaling reduce inhibitory control of excitatory neurotransmission in this critical region, and lower the brain’s ability to regulate stress and anxiety.

The researchers concluded that long-term dysregulation of CRF-FAAH mechanisms in the amygdala keeps anandamide from doing its job. Without anandamide to balance out the system, the brain is primed to react to stress.

Follow-up experiments showed that inhibiting FAAH could blunt CRF’s effects and reduce signs of anxiety in the rats.

Roberto said the next step will be to further study this rat model to better understand relationships between high anxiety and alcoholism. She added that the rat model could also be useful for studying PTSD, where high anxiety is connected to a higher risk of developing alcoholism.

“The results of our study may be useful, not only in understanding the neurobiological basis of alcoholism, anxiety and possibly PTSD, but also in developing more efficacious pharmacotherapies to treat these disorders,” added Ciccocioppo.

The researchers dedicated this study to Parsons. Natividad added a note on Parsons’s influence on the research and on the TSRI campus: “Larry’s guidance throughout the study was critical in bringing together a cohesive story exploring the relevance of endocannabinoid signaling with downstream neural processing in a way that is unique to the field and has translational relevance to the human condition. He serves as a role model for me not only as a scientist, but also in terms of being a good colleague, mentor and friend to those around him. I feel privileged to have been part of his lab, his teachings and mentorship. He will be dearly missed.”

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A LOOK AT AUTISM

News from various researchers and companies looking to manage the spectrum

By DDNEWS Staff

Our overview of recent autism R&D begins with news from Cold Spring Harbor Laboratory (CSHL), discussing work that Prof. Michael Wigler conducted along with Ivan Iossifov from Cold Spring Harbor Laboratory (CSHL) and the New York Genome Center, as well as Andreas Buja, a statistician from the University of Pennsylvania who led the team. Pooling their talents, they tackled a new study of the genetic factors involved in the causation of autism spectrum disorders (ASD), thereby bringing new focus on the impact these illnesses have on motor skills, and more broadly on cognitive function.

“Diminished motor skills appear to be an almost universal property of children with autism,” said Wigler, adding that careful inference from the data suggests to him that the genetic factors causing ASD broadly diminish the brain’s cognitive functions.

These genetic factors are of two types: inherited mutations and de-novo mutations. The latter are changes to the DNA that do not appear in the genetic makeup of either parent and are new in the child, and past research at CSHL and elsewhere has revealed that the presence of these damaging de-novo mutations correlates with lower non-verbal IQ.

The more severe the mutations, the more pronounced the impact.

The new study finds that diminished motor skills, like lower IQ, also correlate significantly with de-novo mutations in ASD, and are an even more sensitive indicator of the damage of a de-novo mutation than IQ, say the researchers.

However, the research also revealed that defining core behavioral components of ASD—impaired social skills and communication—do not correlate with either the presence or severity of de-novo mutations. In other words, a child with autism who has a severe de-novo mutation is no more likely to have severely impaired social skills than is a child with autism for whom no such mutation was found, and who presumably has inherited causal factors.

Nonetheless, the near universality of diminished motor skills in children with autism is an indicator that the factors that cause the core behavioral defects also cause general cognitive dysfunction, Wigler explains. “As such, objective assessment of cognitive function should be a facet of any clinical evaluation of the patient, and included when monitoring therapeutic response.”

Motor skills also factored heavily into a recent study led by researchers at Indiana University (IU) and Rutgers University, where the scientists found that nearly imperceptible fluctuations in movement correspond to autism diagnoses, providing the strongest evidence to date that movement is an accurate biomarker for neurodevelopmental disorders, including autism—and likely other neurodevelopmental disorders.

The study’s results, reported Jan. 12 in the Nature journal Scientific Reports, suggest a more accurate method to diagnose autism. Current assessments depend on highly subjective criteria, such as a lack of eye movement or repetitive actions. There is no existing medical test for autism, such as a blood test or genetic screening.

“We’ve found that every person has their own unique ‘movement DNA,’” said senior author Jorge V. José, the James H. Rudy Distinguished Professor of Physics in the IU Bloomington College of Arts and Sciences’ Department of Physics. “The use of movement as a ‘biomarker’ for autism could represent an important leap forward in detection and treatment of the disorder.”

Unlike diseases diagnosed with medical tests, autism remains dependent upon symptoms whose detection may vary based upon factors such as the person conducting the assessment. The assessments are also difficult to administer to very young children, or to people with impairments such as lack of verbal skills, potentially preventing early interventions for these groups. Early intervention has been shown to play an important role in successful treatment of autism.

“Our work is focused on applying novel data analytics to develop objective neurodevelopmental assessments for autism, as well as other neurodevelopmental disorders,” said Di Wu, an IU Ph.D. student and the lead author on the study. “We really need to narrow the gap between what physicians observe in patients in the clinic and what we’re learning about movement within the field of neuroscience.”

Next, the researchers aim to conduct movement assessments on more people, including more research on the parents of children with autism to better understand the connection between lower parental scores on the movement assessment and their children’s risk for autism.

Remember what we just said a few paragraphs ago about there being no medical test—such as a blood test—for autism? Well, in other news from January, NeuroPointDX, the neurological disorder division of Stmina Biomarker Discovery, maintained that it had validated a first-generation autism diagnostic blood test panel in the Children’s Autism Metabolome Project (CAMP), its clinical study. The study has enrolled 1,100 children, age 18-48 months, over the course of two years. CAMP is the largest study ever conducted that examines the metabolism of children on the ASD spectrum.

“It is not an exaggeration to say that NeuroPointDX will revolutionize diagnosis and precision medicine,” said Elizabeth Donley, NeuroPointDX’s CEO. “By identifying imbalances in the patient’s metabolism, we can diagnose neurological disorders and identify targeted treatments. These interventions may be as simple as modifying diet or dietary supplements, or as complex as developing new drugs to correct the imbalance.”


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Mutations that appear in a child which are not present in either parent—called de-novo mutations—can be important in autism. Severe, gene-disrupting de-novo mutations are thought to be capable of causing the disorder in certain instances, and new research shows that diminished motor skills correlate with the severity of such mutations. More broadly, the study calls attention to the role played by genetics in diminished cognitive functions in children across the autism spectrum.

Indiana University (IU) doctoral student Di Wu directs a volunteer as she touches images on a screen using a device designed to track minuscule fluctuation in the arm’s movement. IU-led research suggests physical movement is an accurate method to diagnose neurodevelopmental disorders, including autism.

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Mutations that appear in a child which are not present in either parent—called de-novo mutations—can be important in autism. Severe, gene-disrupting de-novo mutations are thought to be capable of causing the disorder in certain instances, and new research shows that diminished motor skills correlate with the severity of such mutations. More broadly, the study calls attention to the role played by genetics in diminished cognitive functions in children across the autism spectrum.

Indiana University (IU) doctoral student Di Wu directs a volunteer as she touches images on a screen using a device designed to track minuscule fluctuation in the arm’s movement. IU-led research suggests physical movement is an accurate method to diagnose neurodevelopmental disorders, including autism.

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**DIAGNOSTICS**

**AAI inks deal for prostate cancer diagnostic**

**SAINT-GENIS-POUILLY, France**—An exclusive worldwide license agreement was struck last month between Advanced Accelerator Applications S.A. (AAA), a Novartis company, and Cancer Targeted Technology. The companies will develop and market the investigational new drug product F-18-labeled CTT1057, a ligand of prostate-specific membrane antigen (PSMA) for positron emission tomography imaging of prostate cancer. Though specific financial details were not disclosed, this deal includes an upfront licensing fee, milestone payments and royalties.

Dr. Susanne Schaffert, chairperson and president of AAA, remarked, “This agreement expands our position in the important prostate cancer space. PSMA diagnostics represent an accurate staging and risk assessment tool with the potential to change patient management decisions. CTT1057 is highly complementary to our existing F-18 PET portfolio and AAA is well suited to exploit this opportunity with our proven manufacturing and development capabilities.”

**New reference standard from Horizon Discovery**

CAMBRIDGE, U.K.—Horizon Discovery recently launched its cell line-derived epidermal growth factor receptor (EGFR) Multiplex cell-free DNA (cfDNA) Reference Standard, which enables laboratories and assay developers to optimize, validate and monitor the performance of PCR-based tests, next-generation sequencing and other assays designed to detect EGFR mutations in cfDNA. The reference standard covers 10 of the most clinically relevant mutations predicting responsiveness to EGFR tyrosine kinase inhibitors, including T790M, L858R, C797S and E746-A750del. It is cell line-derived and supplied in a DNA fragment range of 160 base pairs, and comes in a set of four vials and supplied in a DNA fragment range of 160 base pairs, and comes in a set of four vials.

**A novel ‘path’ for Parsortix**

ANGLE and Abbott seek blood test for metastatic breast cancer

**BY RACHEL FLEHINGER**

HIGULDFORD, U.K. & ABBOTT PARK, Ill.—ANGLE plc continues its efforts to couple the use of its Parsortix platform technology with reliable analysis technology partners through a collaboration with global healthcare company Abbott. Through the partnership, Abbott will provide its PathVysion HER2 DNA FISH Probe Kits, which ANGLE will use as it seeks FDA clearance of the Parsortrix system in metastatic breast cancer. The companies determined that a research grant from Abbott to ANGLE was the most straightforward way to allow collaboration to happen. Abbott is a global market leader in DNA fluorescence in-situ hybridization (FISH) testing, which “maps” the genetic material in human cells, including specific genes or portions of genes. It is useful in cancer diagnosis because it can detect genetic abnormalities associated with cancer, and in some cases, predict a patient’s potential response to a specific drug. Abbott’s PathVysion HER2 DNA FISH Probe Kit was the first test approved to show the accurate assessment of a breast cancer patient’s HER-2 status at the DNA level (a key cause of breast cancer) and is widely used by healthcare providers.

**Money for MeMed**

$4M grant awarded to support transfer to manufacturing of MeMed’s pioneering point-of-care platform

**BY MEL J. YEATES**

TIRAT CARMEL, Israel—What if there was an easy, in-office way for doctors to reliably diagnose whether an infection was bacterial or viral? Soon there may be one—MeMed Ltd. has been working on just such a device, and after several studies the company is ready to move into manufacturing.

MeMed announced in early February that it had been awarded a $4,079,159 grant by the U.S. Department of Defense’s Congressionally Directed Medical Research Programs (CDMRP). This award will support MeMed’s pioneering point-of-care platform MeMed’s pioneering point-of-care platform for infectious disease... From Horizon Discovery...
GDF-15 CONTINUED FROM PAGE 45
that investigators have also linked GDF-15 expression to glaucoma disease severity in human patients. The terms of the deal call for Q BioMed to evaluate the feasibility and utility of GDF-15 as the basis of a companion diagnostic for MAN-01, a small molecule treatment for primary open angle glaucoma under development by partner Mannin. Research. Additional terms of the agreement were not disclosed. “The ophthalmology field in general, and glaucoma sector specifically, are currently in an active consolidation and business development cycle,” states Denis Corin, CEO of Q BioMed. “Having access to a truly innovative technology that complements ours—as a companion diagnostic—could greatly enhance the value of the Mannin Research MAN-01 technology.” “We are excited to evaluate this technology and look forward to a new collaborative partnership with a leading institution like Washington University School of Medicine,” Corin adds. Glaucoma is one of the leading causes of blindness worldwide, estimated to affect nearly 100 million people by 2020. The disease is linked to the buildup of pressure within the eye. When this intraocular pressure mounts, it can damage the optic nerve, and if the damage progresses, glaucoma can lead to permanent vision loss. George N. Nikopoulos, president and CEO of Mannin Research Inc., tells DDNews that the collaboration partnership between Q BioMed and Washington University, at this stage, is an opportunity to evaluate the feasibility of commercializing the use of GDF-15. “Our analysis includes patient and physician needs assessments, reimbursement strategy for usage of the biomarker in a clinic and conducting a feasibility analysis on the development pathway of the GDF-15 as a novel biomarker for glaucoma.” Nikopoulos says. “If the evaluation of GDF-15 leads to a potential commercial product, the two parties would formalize a license-based collaborative partnership.” “This platform has the potential to enable a new generation of biomarkers that could make a positive impact upon the treatment decisions for millions of glaucoma patients,” he adds. “There are approximately 60 million patients with glaucoma around the world.”

The potential for utilizing GDF-15 as a biomarker to assess the severity of glaucomatous neurodegeneration was recently reviewed by Washington University’s Dr. Rajendra S. Apte, in the January 2018 Trends in Molecular Medicine article titled “Monitoring Neurodegeneration in Glaucoma: Therapeutic Implications.” Because vision loss in glaucoma is not reversible, therapeutic interventions early in disease are highly desirable,” the article states. “However, owing to the current limitations in evaluating glaucomatous neurodegeneration, it is challenging to monitor the disease severity and progression objectively, and to design rational therapeutic strategies accordingly. As such, in our opinion, molecular biomarker(s) that specifically reflect stress or death of RGCs, and which correlate with disease severity, progression and response to therapy, are highly desirable.”

Progression of glaucoma is typically monitored through a visual field test, but there has not been a reliable way to measure which patients have a high risk of rapid vision loss—until now. Washington University researchers discovered GDF-15 to be a biomarker for glaucoma using an array analysis, which identified chemokines, growth factors, TGF-beta family members and other ligands whose expression increased in the optic nerve crush model of glaucoma, but not in endothelin-induced uveitis or light-induced retinal degeneration models. Washington University also validated GDF-15 in both rat models of glaucoma and in patients, showing that its expression correlates with disease severity. Overall, GDF-15 represents an attractive biomarker for glaucoma with distinctive advantages (i.e., early detection) over conventional clinical tests and has the potential to be a first-in-class diagnostic test. The researchers’ findings of GDF-15 were published online May 4, 2017 in the journal JCI Insight. “Other glaucoma tests are measuring cell death, which is not reversible, but if we can identify when cells are under stress, then there’s the potential to save those cells to preserve vision,” Apte states in the journal article. Apte is also a professor of developmental biology, of medicine and of neuroscience.

“Glaucoma often begins silently, with peripheral vision loss that occurs so gradually that it can go unnoticed,” according to Apte. “Over time, central vision becomes affected, which can mean substantial damage already has occurred before any aggressive therapy begins.” Many patients “start receiving treatment when their doctors discover they have elevated pressure in the eye,” he explains. “These treatments, such as eye drops, are aimed at lowering pressure in the eye, but such therapies may not always protect ganglion cells in the retina, which are the cells destroyed in glaucoma, leading to vision loss.”“Glaucoma specialists attempt to track the vision loss caused by ganglion cell death with visual field testing. That’s when a patient pushes a button when they see a blinking light. As vision is lost, patients see fewer lights blinking in the periphery of the visual field, but such testing is not always completely reliable,” according to the paper’s first author, Dr. Norimitsu Ban, an ophthalmologist and a postdoctoral research associate in Apte’s laboratory. “We were lucky to be able to identify a gene and very excited that this gene seems to be a marker of stress to ganglion cells in the retinas of mice, rats and humans,” Ban says. 
**Diagnostics**

**Dana-Farber/Brigham and Women’s team identifies set of seven microRNAs that could detect early-stage ovarian cancer**

**BY KELSEY KAUSTINEN**

BOSTON—Thanks to the speed and interpretation abilities of artificial intelligence (AI) platforms, they can search through massive databases and cross-reference related literature much faster than existing technologies. As such, AI is seeing increased use in the industry as companies gain more examples of its potential in identifying new avenues and new targets for drug discovery. But a team from the Dana-Farber Cancer Institute and Brigham and Women’s Hospital (BWH) is looking to use AI in another way to advance cancer research— finding new treatments, but for diagnostics.

The researchers singled out a network of seven circulating microRNAs that are associated with the risk of ovarian cancer and are detectable in blood samples. Their work was published online in *eLife* under the title “Diagnostic potential for a serum miRNA neural network for detection of ovarian cancer.”

While microRNAs are well known to play a critical role in ovarian cancer biology, whereas the function of CA125 is unknown and less informative, micro-RNAs have a clear advantage over analytes such as CA125. miRNAs has a clear advantage over analytes such as CA125.

Researchers from the Dana-Farber Cancer Institute (pictured here) and Brigham and Women’s Hospital used artificial intelligence tools to single out a network of seven circulating microRNAs that are associated with the risk of ovarian cancer and are detectable in blood samples.

The Dana-Farber/BWH team found that ovarian cancer cells and normal cells present with different microRNA profiles. micro-RNAs circulate in the blood, which enables their measurement via serum samples. The microRNA levels of 135 women who had not had surgery or chemotherapy were measured via blood samples to produce a “training set” for a computer program, so that it would know how to differentiate between ovarian cancer, benign tumors, non-invasive tumors and healthy tissue. The model that was most capable of differentiating benign tissue from cancerous tissue is known as a neural network model.

“The key is that this test is very unlikely to misdiagnose ovarian cancer and give a positive signal when there is no malignant tumor. This is the hallmark of an effective diagnostic test.”

Dr. Dipanjan Chowdhury, chief of the Division of Radiation at Dana-Farber Cancer Institute

MicroRNAs for earlier diagnosis?

The team also looked for evidence of microRNAs in the cancerous cells, demonstrating that the serum signal was coming from the cancerous tissue. The model that was most capable of differentiating benign tissue from cancerous tissue is known as a neural network model.

Following the promising sample results, the team deployed the microRNA test to predict the diagnoses of 51 patients presenting for surgical care in Lodz, Poland, in which 91.3 percent of the abnormal test results detected with the new model represented ovarian cancer. The test’s negative results correctly predicted absence of cancer approximately 80 percent of the time, similar to the accuracy of a Pap smear test.

The next step in this work will be to monitor how an individual’s microRNA signature changes over time as ovarian cancer risk increases. This will require prospectively collected longitudinal samples from women who can be followed over a period of time.

The key is that this test is very unlikely to misdiagnose ovarian cancer and give a positive signal when there is no malignant tumor. This is the hallmark of an effective diagnostic test,” said Chowdhury.

The team also looked for evidence of biological relevance for the distinguishing microRNAs. They found changes in the quantity of these microRNAs in blood samples collected before and after surgery, suggesting that the microRNA signal decreases after the cancerous tissue is removed. They also took actual patient samples and imaged the microRNAs in the cancerous cells, demonstrating that the serum signal was coming from the cancerous tissues.

This is not the only cancer partnership for the two organizations in recent months. Dana-Farber and the Brigham and Women’s Cancer Center announced in December that they would be launching a program targeting advanced and aggressive thyroid cancers: the Thyroid Cancer 360 Program. This initiative will focus on improving patient outcomes by offering targeted treatments tailored to individuals’ genomics and biology. The program is led by specialists in the Thyroid Cancer Center, and the Center is enrolling patients for the first clinical immunotherapy trial designed for patients with thyroid cancer. **EDITCONNECT: E031826**

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FDA approval for Hologic’s Aptima

**Assay for quantitation of hepatitis B viral load receives pre-market approval**

**BY DDNEWS STAFF**

MARLBOROUGH, Mass.— Late January brought news from Hologic Inc. that the U.S. Food and Drug Administration had granted pre-market approval (PMA) for the Aptima HBV Quant Assay for quantitation of hepatitis B viral load on the fully automated Panther system.

The Aptima HBV Quant assay represents the newest addition to the Panther system’s viral load menu, joining the previously approved Aptima HIVA Quant Assay (for human immunodeficiency virus) and Aptima HCV Quant Dx Assay (for hepatitis C virus). All three new assays use Hologic’s proprietary real-time transcription-mediated amplification, which provides highly sensitive and specific performance. The HBV Quant assay is said to reliably quantitate HBV DNA across all major genotypes A-H.

“This approval represents a milestone for Hologic’s growing virology assay menu,” said Tom West, president of the Diagnostic Solutions division at Hologic. “We now have available on a single system the three major viral load assays that most laboratories are asked to run for patients.”

The Aptima assays run on the Panther system, which provides full, sample-to-result automation and substantially reduces hands-on time with random and continuous access. With the Panther system, laboratorians can now run viral load assays for HIV-1, HCV and HBV in parallel, or even from a single patient sample.

According to the company, the Aptima HBV Quant assay offers “a unique, dual-target approach that delivers accurate quantitation over a broad linear range and tolerates potential mutations in the HBV genome.” The Aptima HBV Quant assay’s linear range is one of the broadest on the market (from 10 IU/mL to 1 billion IU/mL). This helps ensure precise quantitation even for samples with the high viremia often associated with chronic HBV infection.

The HBV assay joins a growing menu of tests available on the Panther system in the U.S. market. In addition to the three viral load assays, the Panther menu includes tests for sexually transmitted infections including chlamydia, gonorrhea, trichomonas, human papillomavirus and herpes simplex virus.

“We hear repeatedly from clinical laboratory customers that menu consolidation is a top priority,” said West. “Offering a robust virology and women’s health menu on a single automated platform will enable them to reach their efficiency goals.”

MeMed announced in early February that it had been awarded a grant of just over $4 million by the Department of Defense to support transition of a prototype point-of-care diagnostic for differentiating viral and bacterial infection toward a final product.

**CONTINUED FROM PAGE 45**

transaction of the prototype point-of-care (POC) platform toward a final product, including transfer to manufacturing and implementation of cloud connectivity.

“This grant will allow us to set up manufacturing processes for our POC platform, ultimately enabling MeMed’s novel blood test that has been clinically validated for differentiating between bacterial and viral infection to reach the patient in a shorter time,” says Dr. Kfir Oved, MeMed’s co-founder and chief technology officer.

According to Oved and company CEO Dr. Eran Eden, the company first began working on this POC platform a few years ago. “Initially, we developed a first-generation product called ImmunoXpert, based on the immune signature MeMed has developed comprising three protein biomarkers (TRAIL, IP-10 and CRP; the ‘TIC’ signature). ImmunoXpert (CE-IVD) is laboratory-based with a turnaround time of around two hours, and has been used to diagnose infections in more than 11,000 children and adults as part of our early access program, which is steadily expanding.

“Having an accurate and validated product is a must, but we knew from the get-go that it’s not enough. For global use, one needs a device that can measure the TIC signature in a very rapid, affordable and user-friendly manner,” they say. “We have been working on this next-generation product, which will provide results within 15 minutes, for the past few years, with the aim of moving into settings like hospital emergency departments and, ultimately, doctors’ offices.”

“The new device is a multi-purpose bench-top platform for quantitative immuneassays that is able to measure proteins reliably even at the picogram per mL level,” Eden and Oved tell DDNews. “In addition to measuring our rapid bacterial versus viral test, the new platform also opens the way to a variety of rapid multiplex-protein measurements at the point of care with lab-quality precision, which has broad application. We are already working to expand the menu of tests that will be available on the POC platform, including novel tests for predicting disease severity and for differentiating between sepsis and SIRS.”

Eden notes, “Fast menu expansion is possible, as our unique platform paves the way to performing a wide range of other multiplex-protein measurements, with laboratory quality, within minutes at the POC—the basis for a panel of tests needed to advance patient care.”

The $4.3 million CDMRP grant complements a $9.2-million contract from the Defense Threat Reduction Agency that MeMed was awarded last year, which is supporting the final stages of prototype development.

MeMed also recently announced completion of a trilogy of clinical studies, two of which were double-blind, conducted over the past seven years. All three trials collectively enrolled 2,796 patients. The latest study, PATHFINDER, published in the official journal of the American Academy of Pediatrics, independently confirmed that MeMed’s novel blood test accurately distinguishes between bacterial and viral infections in children. The test aims to support clinicians in one of the most routine yet challenging clinical dilemmas today—determining whether an infection is bacterial or viral, in order to decide whether to treat or not to treat with antibiotics.

According to Oved and Eden, the POC platform is “a very user-friendly device designed around many different professional and semi-professional end users, where you can basically load the sample into a cartridge, run the test from a touch screen and get the final result within minutes.”

“The company is aiming to soon launch the new POC device in select medical centers towards the end of the year. The new DoD grant will allow us to set up manufacturing processes and reach a wide range of patients in a shorter time,” Eden and Oved conclude.

**EDITCONNECT: E031827**
Presenting a plan for growth

Vetter introduces South Korea’s pharma and biotech community to company management

BY DON NEWS STAFF
SONGDO, South Korea—In early February at an event at its new branch office in South Korea, Vetter’s senior management representatives presented the company’s service portfolio along with its growth strategy for South Korea and the Asia Pacific (APAC) region. In addition, attendees were introduced to Michael Yi, who will manage the office in his role as business development manager for Vetter Pharma International’s South Korea operations. According to Vetter, Yi has “pharmaceutical experience in responsible business development roles” at several companies, and he will report to Chervee Ho in her role as director of key account management.

Innovate UK confident in Cobra

Cobra Biologics receives two separate grants from British innovation funder

BY RACHEL FLEININGER KEELE, U.K.—As biopharmaceutical companies in the United Kingdom are investing heavily in increased production, capacity and partnerships, their internal spending is being boosted with significant investments from Innovate UK. And, it appears, Cobra Biologics’ investment in its U.K. facilities is paying off.

Following the 2017 launch of a £35 million-plan to expand its operations capacity, Cobra Biologics has recently been awarded two separate grants from Innovate UK, which funds innovation across sectors in the United Kingdom to develop ideas and commercialize new technologies. Both grants will help Cobra to further develop its capacity as a leading European contract development and manufacturing organization (CDMO) in cell and gene therapies.

In January, Innovate UK awarded Cobra a £2.6-million grant (about $3.4 million) to be used for continued capital infrastructure investment. That grant will bolster the £13.5-million company expansion announced in 2017 to advance its capability for commercial production of viral vectors and DNA vaccines.
Kicking up clinical capture

**IACT Health selects Alpha Clinical Systems ACS360 e-source platform for trial data capture**

**BY DDNEWS STAFF**

COLUMBUS, Ga. & PISCATAWAY, N.J.—At the end of January, IACT Health, a clinical trial manage-ment company dedicated to streamlining study operations for highly efficient clinical tri-als, and Alpha Clinical Systems, a provider of affordable and comprehensive next-generation e-source solutions, announced that IACT Health has selected Alpha Clinical Systems’ ACS360 e-source platform for clinical trial data capture. Alpha Clinical Systems will provide the fully integrated ACS360 platform, including Study Designer and e-SourceDocx. Using the ACS360 platform, IACT Health will streamline study startup and execution with web-based study design and tablet-based direct e-source data capture. The ACS360 platform is designed to help streamline study operations by providing truly paperless data capture and real-time access to validated study data, dramatically reducing study timelines and costs.

IACT Health is excited to begin working with Alpha Clinical Systems in an effort to further streamline study operations via their next-generation ACS360 e-source platform,” said Christine Senn, chief information officer of IACT Health. “We selected the ACS360 platform because we required an e-source solution that was both comprehensive and affordable, and could deliver real-time, remote access to high-quality study data.”

“IACT Health required a more comprehensive, yet affordable, e-source solution that would streamline and modernize their clinical trials,” said Murthy Gandham, CEO of Alpha Clinical Systems. “We look forward to helping IACT Health deliver high-quality data in real-time via the ACS360 platform.”

Alpha Clinical Systems developed the ACS360 platform to eliminate the challenges of e-source adoption among life-sciences companies. Designed to maximize site efficiency and data quality, the ACS360 platform works with or without existing electronic data capture systems to deliver real-time, remote access to validated clinical trial data. **EDITCONNECT E031831**

**COBRA CONTINUED FROM PAGE 49**

In gene therapy and immuno- oncology programs.

The first Cobra award is part of Innovate UK’s Industrial Strategy, a long-term plan aimed at boosting productivity and earning power throughout the country. One key compo- nent of the overarching strategy is the Life Sciences Sector Deal, which will support a major new life-sciences facility in the Unit-ed Kingdom by MSD (known as Merck & Co. in North America), QIAGEN and other partners like Cobra.

In the wake of the 2017 launch of a £15-million plan to expand its operations capacity, Cobra Biologics recently netted a pair of grants from Innovate UK. Pictured here are representatives of Cobra Biologics at the 2017 Bionow Awards, where Cobra won Company of the Year and Technical Services awards.

“Today’s investment provides strong evidence that a coherent industrial strategy can have a real, tangible impact on eco-nomic activity in sectors that we need to strengthen and grow,” said Sir John Bell, chair of the Life Science Industrial Strategy Advisory Board. “It will drive this sector forward and simulta-neously attract other invest-ments into the U.K.”

This grant, which will allow increased process development, analytics and GMP manufactur-ing, will double the footprint of Cobra’s U.K. site and create 25 to 35 additional jobs.

Peter Coleman, chief execu-tive of Cobra Biologics, com-mented, “Cobra is undertaking a very significant expansion of our viral and DNA manufac-turing capability, and we are very pleased to have received funding from Innovate UK to help accelerate our plans. The investment recognizes Cobra as a leading company in the cell and gene therapy market and provides us, and the U.K., with a unique opportunity to be at the forefront of developing revolu-tionary disease therapies and new treatments for patients.”

Innovate UK also made a sig-nificant investment in Cobra under its Health and Life Sci-ences Programme, through a 16-month collaborative grant of £1.9 million in partnership with contract manufacturing organization Symbiosis Pharma-ceutical Services. Symbiosis specializes in sterile fill finish (the aseptic filling of sterile drugs into sterile packaging), a critical step in biopharmaceuti-cal manufacturing. According to Dr. Ian Camp-bell, director of health and life sciences at Innovate UK, “The U.K. is at the forefront of research into these new thera-pies, but there is a global short-age in viral vector manufactur-ing capacity and we need to act to take advantage of the com-mercial opportunities. Innovate

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MERGE
CONTINUED FROM PAGE 49

our diagnostics portfolio and increase rev-

weves substantially,” said Dr. Richard Lip-

rombe, Proteomics International managing
director. “We see this alliance as adding sig-

ficiant new value to our already successful
Promarker technology.”

The alliance will offer project manage-

ment, certified bio-analysis, trial monitor-
data management and bio-statistical services,
analytical platforms of mass spectrometry and
immunoassay for small and large mol-
eules, sample storage and stability testing—
as well as the development of new methods
and diagnostic tests.

As a contract research organization (CRO),
CPR Pharma has a close relationship with
Phases clinical trial sites across Australia,
biochemist and small to mid-sized pharma-

Two Labs and a life-sciences consulting firm

Meanwhile, in the United States, Colum-
bus, Ohio-based Two Labs, a pharma and
life-sciences services company, announced
Feb. 8 its acquisition of MKO Global Part-
ners, a strategic global life-sciences con-
sulting firm focused on payer strategy,
market access and pricing in the pharma-

cutical and biotech markets.

Two Labs delivers innovative trade and
commercialization services to pharmaceu-
tical manufacturers, while MKO integrates
new capabilities in pricing and market access
strategy.

“The pharmaceutical industry relies on
Two Labs to provide commercialization sup-
port services so that they can focus on
developing new and innovative therapies
that enhance patients’ lives,” according to
Rich Wartel, CEO of Two Labs. “The union
of Two Labs and MKO’s pharma services
expands our total solution suite through the
addition of a highly regarded market access
solutions provider. For both organizations,
culture matters as much as our solutions.
As a result, our clients view us as a strate-
gic partner and an extended part of their
team—not as a vendor.”

Steve O’Malley, a partner at MKO Global
Partners, said, “MKO has enjoyed a 15-year
relationship with Two Labs, and we are
thrilled to be joining the Two Labs family.”

“Each organization views the other as the
logical extension toward the total solutions
suite for market access, and we believe our clients will be
thrilled with the capabilities we will be able to
provide through our new partnership.”

Steve O’Malley of MKO Global Partners

will accelerate our goal of becoming the best-
class solution for risk-based monitoring
and clinical data analytics.

“We look forward to bringing additional
competitive advantages to OmniComm’s cus-
tomers by delivering end-to-end RMB solu-
tions and specialized data analytics expert-
tise,” he adds.

“Adding this RMB and analytics platform to
our existing product lines fills a strong need
for our clients,” said Stephen Johnson,
OmniComm’s president and CEO. “Due to a
common technology stack, the Acuity plat-
form perfectly integrates with our TrialMas-
ter and TrialOne solutions.”

Certa acquires Germany’s BaseCase

Princeton, N.J.-based Certara, a global
leader in model-informed drug develop-
ment and regulatory science, announced
Feb. 1 that it had acquired BaseCase Man-
agement GmbH, a data visualization soft-
ware-as-a-service company headquartered
in Berlin that also has offices in New York.
The acquisition is expected to add strong
visualization and communications capabili-
ties across Certara’s data science decision-
support value chain.

BaseCase, which will join Certara’s Strate-
getic Consulting Services division, will bring
extensive health economics and outcomes
research expertise, and is working in the area
of market access.

As a key element in Certara’s data science
portfolio, BaseCase technology will soon be
leveraged across the company’s industry-

pharmacometrics, mechanistic mod-
eling and regulatory science platforms.

Certa’s solutions span drug discovery
through patient care, its technology increas-
ing the probability of regulatory and com-
mercial success. BaseCase’s interactive plat-
form improves communication to C-suite
executives, physicians, healthcare providers,
payers and health authorities.

“We are delighted that BaseCase is join-
ing Certara and we are looking forward to
expanding the applications for its user-
friendly, mobile communications technol-
yogy,” said Thomas Kerbusch, president
of Certara Strategic Consulting Services.

“BaseCase simplifies communication of
complex data and models,” Kerbusch added.
“BaseCase’s interactive platform will enable
pharmaceutical and medical technology
companies to visualize model results and
large, real-world datasets to make sound
decisions quickly.”

BaseCase Chief Technology Officer
Diarmuid Glynn remarked that, “Certa’s
extensive software development capability
and deep expertise in model-informed drug
development will enable us to further accel-
erate BaseCase’s evolution and growth in this
expanding market space. We have already
identified several expansion projects that
will result from the merger.”

Crown Bioscience joins
Jansen and JSR Life Sciences

Tokyo-based JSR Life Sciences announced
Dec. 20, 2017, the purchase of CRO Crown
Bioscience International, a global drug
discovery and development services com-
pany providing translational platforms to
advanced oncology, inflammation, cardio-
vascular and metabolic disease research—at
a cost of approximately $450 million.

This acquisition marks JSR’s largest life sci-
ences-focused investment to date, extending
the company’s portfolio to include contract
research and development capabilities.

As a premier CRO, CrownBio has indus-
try relationships and a global footprint to
complement JSR’s global presence. Upon
completion of the acquisition, JSR Life Sci-
ences expects to benefit from integrated
capabilities that include research, drug dis-
covets, diagnostics development, cell line
development and process development and
GMP manufacturing.

The strategic merger integrates Crown
Bioscience’s leading translational technol-
y platform, which provides
drug target v

cification, efficacy test-
ing and patient response char-
acterization, with JSR’s in-vitro diagnostic
solutions, GMP manufacturing capabilities
and worldwide distribution networks.

“We are excited to join the JSR family of
companies through this innovation-driven
strategic partnership,” says Dr. Jean-Pierre
Bioscience’s core competencies in preclin-
ical and translational research combined with
JSR’s global footprint, diagnostic solutions
and manufacturing capabilities will provide
a fully integrated solution to help biopharma-
cutical companies get drugs and diagnostics
to market more efficiently.”

The merger is expected to close before
the end of the second quarter of 2018.

Taconic Biosciences provides models and solutions for
every phase of immunotherapy drug development.

Taconic offers an extensive lineup of rodent models and services for preclinical immunology research. This comprehensive suite includes the CEA NOG mouse®, the first and most severely immuno-deficient model on the market. Whether you require humanized mice, advanced strains for syngeneic modeling, a full microbiome portfolio, or genetically humanized CRO, Taconic has the solutions and expertise to propel your research further.

Unparalleled Solutions for Immuno-oncology Research

Taconic Biosciences provides models and solutions for every phase of immunotherapy drug development.

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BURLINGTON, Mass.—An agreement has been signed between Flexion Therapeutics Inc. and GeneQuine Biotherapeutics GmbH under which the former will acquire global rights to GQ-203, a preclinical non-opiod, intra-articular therapeutic under development for symptomatic pain relief and disease modification for osteoarthritis of the knee. Flexion gains an exclusive license to the intellectual property rights for human use of the compound from Baylor College of Medicine. Flexion will pay $2 million to GeneQuine up front, with the potential for additional milestone payments of up to $8.7 million through Phase 2 proof of concept. Should that be reached, GeneQuine could receive up to $54 million in development and global regulatory approval payments, with Baylor receiving a low single-digit royalty on net sales of GQ-203.

REGENXBIO, FUJIFILM announce manufacturing deal

ROCKVILLE, Md.—REGENXBIO Inc. and FUJIFILM Diosynth Biotechnologies have inked an agreement covering the manufacture of REGENXBIO’s lead product candidates, including RGX-314 and RGX-501, to support late-stage clinical development and early commercialization. Per the agreement, REGENXBIO will have guaranteed capacity for the supply of NAV AAV drug substance manufactured under GMP at large scale for three years, with the potential to extend the agreement for another three years.

“With our strong track record of execution, and with facilities and systems that are suitable for late-stage and commercial production, we are well positioned to support the manufacturing needs of REGENXBIO as it continues to move multiple product candidates toward commercialization,” said Martin Meeson, president and chief operating officer of FUJIFILM Diosynth Biotechnologies.

NHGRI: Seeing 2020

Strategic plan aims to engage experts and diverse communities to identify paradigm-shifting areas of genomics

BY MEL J. YEATES

BETHESDA, Md.—On Feb. 12, The National Human Genome Research Institute (NHGRI) of the U.S. National Institutes of Health launched a round of strategic planning to establish a 2020 vision for genomics research aimed at accelerating scientific and medical breakthroughs. In developing the strategic plan, the institute will engage experts and diverse public communities to identify paradigm-shifting areas of genomics in an effort to expand the field into new frontiers and enable novel applications to human health and disease.

“In developing an updated vision for genomics, we aim to be a driving force for highly impactful and broadly applicable research aimed at accelerating scientific and medical breakthroughs,” says Dr. Eric Green, director of NHGRI, of a new effort to fund genomics research.

Supporting science startups

Elsevier welcomes six biotech and pharma companies to The Hive

BY ILENE SCHNEIDER

NEW YORK—Elsevier, the global information analytics business specializing in science and health, announced that six startup companies have been selected from more than 150 global applicants on The Hive, Elsevier’s innovation initiative for biotech and pharmaceutical startups. The Hive, which first launched in 2016 with four startups selected to take part, engages the global pharma community via a content featuring the participants, which will be promoted throughout Elsevier’s online and social networks.

Elsevier provides digital solutions and tools in the areas of strategic research management, R&D performance, clinical decision support and professional education for 18 months to startups working on a wide range of technologies and discoveries. Companies were selected for their commitment to cutting-edge science in emerging areas of research and potential to impact how future treatments are researched and developed.

ON THE CUTTING EDGE

A roundup of instrumentation, software and other tools and technology news

BY JEFFREY BOULEY

MINNEAPOLIS—Late last year, Advanced Cell Diagnostics (ACD), a Bio-Techne brand, celebrated a milestone in the adoption of its RNAseq in-situ hybridization (ISH) technology. Reaching 1,000 publications and increasing to an average of more than one publication per day, papers using RNAseq now feature regularly in top-tier journals, the company notes, marking this as “clear evidence that scientists are applying RNAseq ISH as a robust and sensitive assay that yields the high-quality data necessary for cutting-edge studies.”

A recent surge—400 publications featuring RNAseq in 2017 alone—included a notable increase in pharmaceutical and biotechnology industries. Authors of recent publications include researchers at Bayer, Merck and Eli Lilly.

Reflecting confidence in the assay, ACD says its ISH technology is also becoming a primary assay used in research rather than a secondary confirmatory assay, citing as an example that a recent Nature publication, “Stromal R-spondin orchestrates gastric epithelial stem cells and gland homeostasis,” used more than 40 RNAseq probes to elucidate the mechanism by which epithelial cells regulate and shape their environment.

In addition to the growing number of industrial publications in immunology, cancer, gene therapy and many orphan diseases development programs, RNAseq is also being used in new areas of academic research, ACD notes. These fields include neurology, neurodegeneration and neuroscience.
FDA approves record number of personalized medicines in 2017

BY DDNEWS STAFF
WASHINGTON, D.C.—The Personalized Medicine Coalition (PMC) in late January released a report documenting the record number of new personalized medicines the U.S. Food and Drug Administration (FDA) approved last year, making 2017 the fourth consecutive year that personalized medicines have accounted for more than 20 percent of all new drug approvals.


Specifically, the report lists a total of six regulatory precedents FDA set last year, as follows: (1) A record number of 16 personalized medicines approved as new molecular entities; (2) the approval of first three gene therapies; (3) the first approval of a tissue-agnostic indication for cancer therapy; (4) the first authorization for marketing of health-related genetic tests directly to consumers; (5) the first approval of a personalized medicine biosimilar; and (6) the first FDA/CMS joint approval and coverage decision for a next-generation sequencing test.

PMC President Dr. Edward Abrahams said the precedents demonstrate how personalized medicine has reshaped drug development in the decade since 2007, when targeted therapies accounted for less than 10 percent of new drug approvals.

As the PMC points out, an influential article published in 2007 in the Harvard Business Review titled “Realizing the Promise of Personalized Medicine,” for example, suggested that FDA was not yet committed to the paradigm. The pharmaceutical industry, the article noted, was at that time hesitant to develop medicines for smaller patient populations, preferring instead to develop “blockbuster” medications that could earn approval for one-size-fits-all applications.

This obviously is no longer true, the PMC remarks, though there remain many obstacles—notably regarding regulation, reimbursement, access and clinical adoption—that complicate the commercialization of personalized medicine products.

“Despite myriad challenges, the diagnostic and pharmaceutical industries are deeply invested in making healthcare more effective and efficient by developing products that guide treatments to only those patients who will benefit from them,” Abrahams explained. “As this report shows, FDA is increasingly committed to supporting that effort.”

The PMC promotes the understanding and adoption of personalized medicine concepts, services and products to benefit patients and the health system.

“Despite myriad challenges, the diagnostic and pharmaceutical industries are deeply invested in making healthcare more effective and efficient by developing products that guide treatments to only those patients who will benefit from them. As this report shows, FDA is increasingly committed to supporting that effort.”

Dr. Edward Abrahams, president of PMC
CRISPR (an acronym for clustered regularly interspaced short palindromic repeats) is a technology derived from a bacterial immunity system for altering chromosomal sequences in situ in a cell in combination with a bacterially derived protein called Cas9, which is expected to have a game-changing effect on next-generation genetic engineering efforts in a wide variety of fields (hailed as the “Breakthrough of the Year” for 2015).

CRISPR provides a mechanism for inserting or deleting specific DNA sequences using CRISPR-associated targeting RNAs and the Cas9 RNA-guided DNA endonuclease enzyme. It provides for the first time the type of specificity for altering DNA that the polymerase chain reaction (PCR) provided a generation ago for amplifying specific DNA. Accordingly, patent ownership is a valuable commodity, and while there are now several groups of inventors developing the technology, there were two principal players at its inception. One group represents inventors from the University of California, Berkeley (Jennifer Doudna) and the University of Vienna (Emmanuel Charpentier), and the other group is The Broad Institute/MIT and Harvard University (Zhang and colleagues). In the United States, an expensive and hotly contested proceeding before the U.S. Patent and Trademark Office termed an interference determined that the Broad/Harvard inventors were entitled to embodiments of the invention directed to eukaryotic cells (including human cells), and the Berkeley/Vienna inventors were entitled to embodiments with no restrictions as to cells in which the modifications are made. This determination remains on appeal.

On Jan. 17, the European Patent Office (EPO) came to a different decision, based in part on the more stringent priority rules applied under the European Patent Convention. The Opposition Division (OD) of the EPO revoked in its entirety The Broad’s European Patent No. EP 277,1468, which had been opposed by Novozymes A/S, CRISPR Therapeutics AG and several other entities anonymously.

The revoked claims were directed to a CRISPR system comprising chimeric RNA polynucleotides made up of a guide sequence of between 10 to 30 nucleotides in length, capable of hybridizing to a target sequence in a eukaryotic cell, as well as additional helper sequences having a particular arrangement, and a Type II Cas9 protein that complexes with the polynucleotide sequences to effect intracellular genetic engineering (replacement or deletion of specific gene sequences).

The basis for this decision (which was released only as a preliminary opinion last year) is that the European Patent was not entitled to the earliest claimed priority date, to a U.S. provisional application naming not only MIT and Harvard inventors but also inventors from The Rockefeller University. In the United States, in contrast, these provisional applications were filed in the name of the inventor.

Under European law, in situations like these, the application that is the basis for the granted European patent must be filed in the name of all assignees, or at the time of filing the right must be transferred by assignment to the named applicants. Neither provision of European priority law was satisfied by the Broad, and thus the OD held that the European patent was not entitled to this priority claim. This made available prior art that precluded patentability of the granted claims, and they were thus revoked.

The Broad argued that this was a misapplication of the law and that priority should be determined based on the national law of the priority document. Here, the earlier provisions applied (in the Broad’s view) disclosed more than one invention, and the invention pursued in the granted European patent was invented by the Harvard, MIT and Broad inventors, not by the Rockefeller inventor. Accordingly, those inventors through their assignees properly claimed the priority right to what was disclosed in those provisional applications and contained in the granted European patent. The Broad filed a notice of appeal based on these arguments. Paradoxically, just two days before the OD’s decision, the Broad won an arbitration against Rockefeller, whereas U.S. patents claiming priority to some of the same provisional applications were determined to properly exclude the Rockefeller inventor and to quiet title to these patents with the Broad et al. and not Rockefeller. This occurrence was not considered by the OD (who deemed its submission two days prior to oral proceedings to be untimely) and may not be particularly relevant to the Broad’s appeal, insofar as it is another example of the differences between U.S. law and the EPC regarding a priority determination. But in view of the financial interests at stake, the answer to this question will be extremely significant to the Broad and the development of this technology in Europe. »

BY KEVIN NOONAN

Kevin Noonan is a partner with the law firm McDonnell Boehnen Hulbert & Berghoff LLP and represents biotechnology and pharmaceutical companies on a myriad of issues. A former molecular biologist, he is also the founding author of the Patent Docs weblog, http://patentdocs.typepad.com/.
Elsevier, a global information analytics business specializing in science and health, announced that six start-up companies have been selected from more than 150 global applicants for this year’s installment of The Hive, Elsevier’s innovation initiative for biotech and pharmaceutical startups.

**HIVE CONTINUED FROM PAGE 52**

In addition, P-Pharma, from France, bridges the gap between academic discoveries and the pharma industry, helping to mature early-stage technologies from the drug discovery level to clinical phase and commercialization. Beacon Discovery, from San Diego, composed of scientists who have worked together for more than a decade, leverages academic and pharma partnerships to advance research around translating G-protein coupled receptors into new therapeutics.

Finally, Sigilon Therapeutics of Cambridge, Mass., develops treatments based on a platform enabling a new therapeutic modality for chronic diseases that are currently treated with intermittent injection or infusion, and Unum Therapeutics, also in Cambridge, develops novel immunotherapy products based on its universal antibody-coupled T cell receptor to treat many types of cancer.

“As the pharma ecosystem grapples with how to incorporate artificial intelligence into R&D, or how to accelerate the discovery of new biologics and immunotherapies, startups around the globe are playing a pivotal role,” said Betsy Davis, senior strategic marketing manager at Elsevier. “We received more than three times the number of applications than in 2016, underlining the importance that startups place on the role of discovery solutions in innovation.”

She added, “This year, to demonstrate the vast contribution of startups in the origin of drug discoveries, we will especially focus on helping these companies close the gap between concept and commercialization, particularly for startups from academic backgrounds. We look forward to sharing the stories of these dynamic, exciting biotech startups with a global audience.”

According to Christy Wilson, global leader of Life Sciences and Healthcare Solutions at Elsevier, “All of the applications we received showed that startups around the globe are doing some really exciting work. Choosing just six was extremely hard ... Each company demonstrated a commitment to addressing an area of high need in therapeutics and represented cutting-edge approaches to research—including how automation and artificial intelligence can support better decisions and accelerate their route to market.”

Wilson concluded, “Following the success of our Hive projects in 2016 and 2017, demonstrated by the increase in applications we had this year, we plan to run The Hive again in 18 months with another intake of startups. One thing The Hive offers is a far-reaching platform to share success stories, and we plan to further share and amplify the successes of our Hive participants to the wider industry.”

Christy Wilson, global leader of Life Sciences and Healthcare Solutions at Elsevier

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Advanced Cell Diagnostics celebrated a milestone recently as its RNAseq technology reached a point where it had featured in 1,000 scientific publications.

EDGE
CONTINUED FROM PAGE 52

to existing customers, we are trying to provide the best treatment outcomes for patients suffering from cardiovascular diseases, and we are delighted that they have chosen to collaborate with us to support the generation of real-world evidence in this space to better understand the complexities of the disease. These types of projects are ideal for frameworks and are supported by state health authorities, which can help us understand the strategies for reviewing and analyzing the data.

Real-world evidence solutions for Pfizer in cardiovascular disease

BASIL, Switzerland & BOSTON—BC Platforms, a leader in genomic data management and analytics, announced in February that Pfizer Finland will be using its technology solutions and research platform, including BCRQUEST.COM, to study data in cardiovascular diseases. The services will be used to analyze anonymized data from Turku University Hospital and other healthcare providers to generate real-world evidence in atrial fibrillation patients. Microsoft will provide the cloud infrastructure for indexing and accessing the information globally through the Microsoft Azure cloud platform.

Cardiovascular diseases are a leading cause of mortality in the world and the incidence is rising due to an aging population. The diseases are complex, and therefore we need data to fully understand and provide the best treatment outcomes for patients,” noted Jaukkio Parkkimo, country medical director at Pfizer. “We believe that combining our expertise in treatment of cardiovascular diseases with BC Platforms’ advanced genomic and clinical data management solutions through BCRQUEST.COM, we can gather and analyze important real-world evidence to generate optimal patient outcomes.”

Samu Kurki, lead scientist at BC Platforms, commented: “Pfizer is one of the leaders in providing treatment solutions for patients suffering from cardiovascular diseases, and we are delighted that they have chosen to collaborate with us to support the generation of real-world evidence in this space to better understand the complexities of the disease. These types of projects are ideal for frameworks and are supported by state health authorities, which can help us understand the strategies for reviewing and analyzing the data.”

BC Platforms, a world leader in genomics research.

In addition, GATK4 includes tools that take advantage of machine learning, including neural network algorithms, which improve the accuracy in discovery of variants.

Over the last 12 months, software engineers at the Intel-Broad Center for Genomic Data Engineering have also incorporated major performance optimizations into GATK4.

“We completely reengineered GATK4 to optimize speed, scale and flexibility, while maintaining the best practices pipelines and high quality of data output that have been the standard for genomics research around the world,” said Eric Banks, senior director of the Data Sciences Platform. “Already, GATK4 has been put to the test internally at the Broad Institute for six months—including by processing the 24 terabytes of sample data, we can now leverage Ion AmpliSeq technology for research use. Illumina will sell the product directly to its customers under the name AmpliSeq for Illumina. Thermo Fisher will continue to sell Ion AmpliSeq chemistry for both in-vitro diagnostic and research-use-only applications to its Ion Torrent SRS customers, and retain the right to make the technology available on other next-generation sequencing platforms.

“Thermo Fisher expects standardization of the AmpliSeq technology to have a profound impact on disease research and encourage greater collaboration among disease communities,” said Joydeep Goswami, president of clinical next-generation sequencing and oncology for Thermo Fisher Scientific. “This agreement, a much larger base of research customers can now leverage Ion AmpliSeq technology’s benefits, while Thermo Fisher continues its commitment to Ion Torrent targeted sequencing solutions for the research market and accelerates its focus and forward momentum in the clinical space.”

This partnership represents a significant step forward enabling a high-performing, flexible amplification chemistry for use on Illumina’s market-leading portfolio of sequencing systems, said Mark Van Oene, chief commercial officer for Illumina. “By expanding access to AmpliSeq chemistry to existing customers, we are enabling them to do even more with their systems.”
progress that empowers others in the field and helps to improve the lives of all people,” says Dr. Eric Green, NHGRI’s director, who launched the current round of strategic planning at the 82nd meeting of the National Advisory Council for Human Genome Research.

In the past, NHGRI has often taken an “all things genomics” approach to strategic planning. But many applications of genomics to specific areas of biology and human disease have matured considerably, evolving into important specialized areas in their own right.

“The breadth and depth of genomics across the biomedical research landscape are rapidly expanding,” Green points out. “At this time, it is critical that NHGRI stay laser-focused on pioneering genomics endeavors, rather than casting a wide net that includes areas well-studied and heavily supported by other organizations.”

“[Areas] that are well-established and/or being sufficiently funded by others will likely be de-emphasized during NHGRI’s strategic planning process—not because they are unimportant, but rather because they are not in need of NHGRI’s unique capabilities and attention. In some cases, these will reflect areas that the institute once emphasized and funded, but for which progress now allows the Institute to cede leadership, strategic planning and funding to others. Two such examples include cancer genomics and microbiome research, because of their strong support by others in the scientific community.”

The process will culminate in the publication of the new strategic plan in October 2020 to commemorate the 30th anniversary of the launch of the Human Genome Project, the international effort that first mapped a complete sequence of the human genome.

When asked what he believes the impact will be on researchers who focus on the areas of research being deemphasized, Green says, “Cancer genomics, microbial genomics and microbiome research—several very important (and ‘hot’) areas of genomics—are now blossoming. At some point in the past, NHGRI was involved in helping shape and support research in each of these areas. Over time, these areas have grown and matured substantially, attracting other major funders, who now lead and support the associated research.”

“These are…areas of genomics that are critically important and should continue to expand, but will not be tackled directly as part of NHGRI’s strategic planning process. In fact, these areas deserve their own dedicated strategic planning that engages individuals with appropriate expertise (and, in many cases, such planning is already underway),” continues Green. “At this time, we are awaiting input from the community about which areas will (and will not) be critical to pursue with NHGRI attention and funding over the coming years.”

NHGRI expects to prioritize discussions in emerging areas of genomics that are not well defined, will benefit from significant investments and are not specific to particular diseases or physiological systems. These include broadly applicable areas such as genomic technology development; using genomic information in patient care; and the ethical, legal and social implications of genomics, among others.

“The 2020 strategic planning process will identify the major areas of focus for NHGRI funding moving forward. We will concentrate on areas that we deem are at the ‘forefront of genomics’ as it pertains to human health and disease. There are a number of major areas that have yet to be well defined and lack significant investments. These newly emerging areas will get high-priority attention during the institute’s strategic-planning process,” Green tells DDNews.

“Often ‘agnostic’ to particular diseases or physiological systems, these areas will be particularly appropriate for NHGRI’s stewardship and funding.”

Prototype examples of these areas include genomic technology development; genomic variation and its functional consequences; epigenomics; interactions between the genome and the environment; general and generic aspects of (and barriers to) uses of genomic medicine in clinical care; research and clinical training in genomics; policy development and implementation to enhance data sharing; and ethical, legal and social implications of genomics, he elucidates, adding: “The strategic planning process will also invest attention into opportunities in the study of rare and common diseases, as well as computational genomics and data science.”

Initially, NHGRI plans to frame the strategic discussions in five focus areas: basic genomics and genomic technologies; genomics of disease; genomic and precision medicine; genomic data science; and society, education and engagement. NHGRI will seek input from a variety of stakeholders, including the scientific and medical communities, non-profit and private sectors, patient groups and the public.

The institute will provide multiple ways for those interested to provide input and to help shape the 2020 strategic plan, including workshops, town halls, social media conversations and satellite meetings at scientific conferences. Anyone can now submit comments on the institute’s dedicated strategic planning website on genome.gov, and follow conversations on Twitter and Facebook using the hashtag genomics2020.

“All elements of the strategic planning process will feed into the final NHGRI’s 2020 strategic plan for genomics. At this time, there is no formula for weighting any of these elements [input and feedback from social media, workshops, etc.] higher than others,” concludes Green. “We do encourage members of the scientific and lay communities to join us at one of our town halls, as those are good opportunities for cross-discussion amongst the communities involved in genomics.”

Dr. Eric Green, director of NHGRI

“The breadth and depth of genomics across the biomedical research landscape are rapidly expanding. At this time, it is critical that NHGRI stay laser-focused on pioneering genomics endeavors, rather than casting a wide net that includes areas well-studied and heavily supported by other organizations.”

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

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ApconiX scientist first outside U.S. to win prestigious award

CHESHIRE, U.K.—The 10th person to receive the U.S.-based Society of Toxicology’s Founders Award given out near the end of 2017—Prof. Ruth Roberts, co-founder and director of nonclinical safety company ApconiX—also became the first scientist not based in the United States to receive the prestigious international award for professionals specializing in drug and chemical safety.

The Founders Award, given out by the Society of Toxicology (SOT) is presented for “outstanding leadership in fostering the role of toxicological sciences in safety assessment.” Roberts joined more than two dozen other professionals acknowledged by the SOT with awards in December.

“Ruth Roberts’ vision of integrated research and drug safety programs covering several modalities and methodological approaches has served her well,” said William Slikker Jr. of the U.S. Food and Drug Administration National Centre for Toxicological Research, who is a past president of the SOT. “Her strategies have improved human health as their goal and rely on the synthesis of basic research and clinical application to achieve a new level of understanding.”

The SOT, a professional and scholarly organization of more than 8,200 scientists, has represented toxicology practitioners and recognized achievements in the field for more than half a century.

Roberts, who helped found ApconiX in 2015, recently was awarded “Start-up of the Year” by U.K.-based BioNow, and she is also chair and director of drug discovery at the University of Birmingham in the U.K. Previously, she worked in senior roles in regulatory safety, drug discovery and development and scientific strategy for companies such as AstraZeneca, ICI, Syngenta and Aventis.

Prof. Ruth Roberts of ApconiX is the recipient of SOT’s 2017 Founders Award—a first for a non-U.S.-based scientist.

Bio-Techne awards $40K research grant to innovative cancer researcher

MINNEAPOLIS—Late last year, Advanced Cell Diagnostics (ACD), a Bio-Techne brand, announced the winner of its “RNAstitcher ISH Get Hybridized” giveaway designed to recognize individuals who are doing groundbreaking research with RNAstitcher in situ hybridization (ISH) technology. The winner, Dr. Andreas Behren, group leader for cancer immunology at the Olivia Newton-John Cancer Research Institute (ONJCI) Institute in Melbourne, Australia, received the grand prize—a $40,000 research grant.

Several thousand researchers from around the world participated in the year-long giveaway by describing their research and its impact, as well as a potential role for RNAstitcher ISH. In addition to the grand prize, ACD also gave away eight $2,000 grants during the year, donating a total of $56,000 to research.

Behren was awarded the grand prize in recognition of his research on the interplay between the immune system and cancer, classifying immune cells and their role in the tumor microenvironment.

“I am honored to be selected for this award,” Behren commented that: “The information from our research could be a step forward in understanding why some tumors respond to immunotherapy and others don’t. When I heard I’d won the giveaway, I immediately thought about the possibilities for RNAstitcher in our projects. There isn’t money to develop or adjust novel assays or methods to specific questions, so I am delighted and grateful to now have this opportunity with the ACD research grant.”

“Using RNAstitcher, we hope to track and visualize antigen-specific T cells in situ and profile their activation status and immune-checkpoint expression pattern. With this information, it would be possible to determine the activation profile of tumor-specific T cells and their location within the tumor microenvironment in FFPE tissues. Hopefully, this will reveal novel targetable mechanisms that contribute to resistance to immunotherapies.”

Vilcek Prizes recognize immigrant scientists

NEW YORK—The Vilcek Foundation in February announced the winners of the 2018 Vilcek Prizes in Biomedical Science. Awarded annually, the prizes call attention to the breadth of immigrant contributions to science in the United States. In parallel, the Vilcek Foundation also awards prizes for immigrant accomplishments in the arts.

“The collective discoveries of this year’s prize winners are truly exceptional,” says Jan Vilcek, chairman and CEO of the foundation.

“They have wide-ranging implications in both basic and translational science and include novel technologies that, until recently, were not even within the realm of imagination. They are even within the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. They are even among the realm of imagination. 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What you may have missed online from DDNews

www.ddn-news.com

Following is a small sampling of the many stories you can find at www.ddn-news.com. To read the full articles, search for their Editconnect numbers at our website, using the “Search our archives” box at the top left of the home page. This time around, we’re focusing on the “Bench Press” stories we post online, which focus on the research more than the business of pharma/biotech.

PEOPLE & PROMOTIONS

BIA Separations

Pete Gagnon

Chief Scientific Officer

AJDOVŠČINA, Slovenia—BIA Separations, a biochromatography development and manufacturing company, has appointed Pete Gagnon as chief scientific officer (CSO). In his new role, he will drive the company’s new product and applications development, with a focus on the purification of products for gene therapy, oncolytic vaccines and exosomes. He was previously president and CSO of Validated Biosystems and brings more than 30 years of experience in the biotech industry, where he is known for his work in the development of purification technology for the manufacture of biologics, including viruses and exosomes. The majority of his experience has been gained in the development of commercial purification procedures for recombinant human therapeutics.

Bellicum Pharmaceuticals

William Grossman

Chief Medical Officer

HOUSTON—Early February brought news that Bellicum Pharmaceuticals Inc., which develops novel, controllable cellular immunotherapies for cancers and orphan inherited blood disorders, had named Dr. William Grossman as its chief medical officer—he joins Bellicum from Genentech/Roche. “We are excited to have Bill join Bellicum. His expertise in the development of cancer immunotherapies and combinations will strengthen our team as we advance and expand our CAR-T and TCR pipeline and prepare for the regulatory filing and potential commercialization of BPX-501 in Europe,” said Bellicum’s president and CEO, Rick Fair.

Almac Group

Stefan Mix

Head of Biocatalysis

CRAGAVON, Northern Ireland—Almac Group, a global contract development and manufacturing organization, announced early this year the appointment of Stefan Mix to the position of head of biocatalysis. Mix joined the Almac Sciences business in April 2005 as a chemist working in the lab on process development projects for chiral materials and has been part of the biocatalysis team since its beginning. He has gained broad industrial experience including applications of biocatalysis, crystallization development, process development for chiral building blocks and active pharmaceutical ingredients, as well as technology transfer to manufacturing network partners, and was promoted to biocatalysis team leader in 2012. All this time he has played a significant role in the development of Almac Sciences’ Biocatalysis Technology platform, which has seen rapid growth and has multiple applications across a range of project scales and industries.

Glythera appoints chief scientific officer and strengthens SAB

NEWCASTLE, U.K.—In mid-January, Glythera Ltd., a next-generation antibody-drug conjugate (ADC) development company, announced the appointment of Dr. Robert Lutz as chief scientific officer. He will lead the advancement of Glythera’s portfolio of ADCs in the treatment of difficult-to-treat cancers. In addition, Glythera has appointed Dr. Jon Roffey to the company’s scientific advisory board (SAB).

With more than 25 years’ experience, Lutz was previously vice president of translation research and development at ImmunoGen Inc., where he was responsible for all early-stage ADC development programs and gained further experience in directing the clinical pharmacology, biomarkers, pharmacology and toxicology departments. While at ImmunoGen, he was responsible for bringing eight of ImmunoGen's candidate ADC products into development and was the research lead for Kadcyla.

Roffey joins Glythera’s SAB from Cancer Research Technology, Cancer Research UK’s commercial partnerships team, where he has been working since 2006, initially as medicinal chemistry group leader and, latterly, with responsibility for forging drug-discovery alliances between academia and industry. As a medicinal chemist by training, Roffey has had active involvement in a wide variety of therapeutic areas, including the development of ADCs in cancer.

Poseida Therapeutics

Martin Giedlin

Vice President, Technical Operations

SAN DIEGO—Early February saw Poseida Therapeutics Inc. announce that Dr. Martin Giedlin had joined the company as vice president of technical operations. Giedlin brings significant expertise in cell therapy process development, manufacturing and strategy in immunotherapies. Most recently, he led the process development teams that generated the clinical and commercial manufacturing process in support of the first FDA-approved CAR-T cell therapy, Novartis’ Kymriah (CT019).

Ablynx

Robert Friessen

Chief Scientific Officer

GENT, Belgium—Ablynx recently appointed Dr. Robert Friessen to the position of chief scientific officer, where he will lead the company’s scientific, research and technology activities and become a member of the executive committee. He succeeds Dr. Antonin de Fougerolles, Ablynx’s previous CSO, who left the company last year to become CEO at Evos Therapeutics.
JAX releases new online mini-courses to address research challenges

The Jackson Laboratory

JAX has announced the release of two new online courses:
- **“Diversity Outbred Mice”** provides an overview of genetically diverse mouse models, the Collaborative Cross (CC) and the Diversity Outbred (DO).
- **“Cre-lox Technology in Mouse Modeling”** is an introduction to using the Cre-lox system to genetically engineer mice for human disease modeling.

Hundreds of researchers have accessed our online MiniCourses, which provide digital, on-demand access to educational modules based on our renowned in-person courses, conferences and workshops. An easy-to-use online interface enables students to proceed at their own pace. For a limited time, JAX is offering free access to the first online MiniCourse, “History and Development of the Mouse Model System.” MiniCourses are planned in everything from the basics of mouse genetics to CRISPR, so stay tuned for the release of additional modules and programs.

See us at AACR Booth # 2426
The Jackson Laboratory
https://www.jax.org/education-and-learning/course-and-conferences/minicourses

Free MojoSort magnet offer

BioLegend

Evaluate BioLegend’s MojoSort system with a complimentary 5 mL size magnet (restrictions may apply). E-mail sales@biolegend.com to get started. MojoSort is our magnetic cell separation system for the isolation and purification of cells from heterogeneous populations. Cells can be isolated by positive or negative selection. Either way, the separated fractions of cells can be used for downstream applications.

See us at AACR Booth # 2149
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The SR-X Ultra-Sensitive Biomarker Detection System

Quanterix

The Quanterix SR-X Ultra-Sensitive Biomarker Detection System is the latest instrument powered by Simoa (single molecule array) technology, offering researchers access to ultra-sensitive and multiplex detection capabilities in a compact and affordable system. The SR-X is designed for multiplex detection of up to six analytes per well, with low volume requirement to increase productivity and throughput, while conserving precious samples.

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Power up your discovery pipeline with CRISPR Horizon Discovery

Combine whole-genome CRISPRi (interference) and CRISPRa (activation) screening to understand complex gene networks and drug responses. Our latest cutting-edge tools provide precise and sensitive screening solutions. They power discovery and drug development programs by offering the highest quality and most consistent confidence in screening results.

See us at AACR Booth # 3220
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CLARIOstar: The most flexible microplate reader

Bmg LABTECH

The CLARIOstar from Bmg LABTECH is a super flexible plate reader, equipped with a unique LIF monochromatic technology. A combination of monochromators, filters and spectrometer means that it does not compromise on sensitivity or flexibility. As well as its high performance in all detection modes, the CLARIOstar’s versatility also makes it ideal for cancer research.

See us at AACR Booth # 3313
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IEG offers hands-free multichannel pipetting

INTEGRA Biosciences

INTEGRA has launched the ASSIST PLUS pipetting robot to put automated pipetting within reach of virtually every lab. Using any INTEGRA electronic multichannel pipette, this compact system offers laboratory automation at an affordable price, providing reproducible and error-free processing while eliminating repetitive manual pipetting tasks.

See us at AACR Booth # 2227
INTEGRA Biosciences
www.integra-biosciences.com

The Mini-Extruder by Avanti Polar Lipids

MilliporeSigma

The Avanti Mini-Extruder allows researchers and scientists to prepare large, unilamellar vesicles by extrusion (LUVET) in an efficient, rapid manner. We are offering a promotion on the Avanti Mini-Extruder, which includes the sale of a LUVET kit for $599.99.

See us at AACR Booth # 1719
STEMCELL Technologies
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huNOG mice

Taconic Biosciences

Taconic Biosciences’ humanized NOG mice are engineered with human CD3+ hematopoietic stem cells stably develop multiple cell lineages by 12 to 16 weeks post-engraftment; all mice are ≥25 percent HCD45+ in peripheral blood. Custom options for huNOG generation and assessment of engraftment are available.

See us at AACR Booth # 705
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https://www.taconic.com/find-your-model/precision-research-models/-immune-system-engrafted-mice/

EnVision Multimode Plate Reader

PerkinElmer

The EnVision multimode plate reader provides exceptional speed, sensitivity and ultra-high throughput across all detection technologies. Tried and tested, it gives robust performance and reliable data for high-throughput screening, time after time. The new 3105 model delivers even higher sensitivity for TRF applications, and the enhanced security software option facilitates results management.

See us at AACR Booth # 2512
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ddPCR screening for mutations in KRAS, NRAS and BRCA from Lonza.

Bio-Rad Laboratories

New ddPCR Multiplex Mutation Screening Kits detect mutations in BRCA, KRAS and NRAS genes associated with a number of cancers including lung, colorectal, ovarian, thyroid, melanoma, breast and pancreatic. The kits are predesigned, fully wet-lab validated assays that screen for multiple key cancer mutations and wild type in a single reaction. The screening kits work with DNA obtained from both FFPE and liquid biopsy sources.

See us at AACR Booth # 1031
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www.bio-rad.com/MutationKits

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

For more information, visit www.ddn-news.com
Lentiviral particles enable you to focus on gene delivery

Origen

Delivering genes into hard-to-transfect or primary cells? Lentivirus is a powerful gene delivery tool, enabling you to focus on gene delivery, not gene delivery. Genome-wide Lenti-Drop® and Lenti-shRNA products are available from Origen. Highly efficient Lentiviral packaging and titer kits are also available. See us at AACR Booth # 2339

See us at AACR Booth # 1935

www.origene.com/products/cdna-clones/lentiviral-particles

Cytomat SkyLine microplate storage and sequential delivery device

Thermo Fisher Scientific

The Cytomat SkyLine can hold up to 728 microplates and/or lids in 14-stackers and provides rapid access in under 12 seconds per microplate. The built-in sequencer ensures reliable delivery of a wide range of labware, including items that traditionally do not stack and separate well, such as lids, folded microplates and sealed microplates. Plates can be return-loaded into the device and stored at ambient conditions, eliminating the need for additional storage devices. This option allows up to 190 m of transfer position range for flexible placement in laboratory automation systems.

Thermo Fisher Scientific

www.thermoshake.com


Optimize NGS performance with QG AATI

Understanding nucleic acid quality is essential for optimal next-generation sequencing (NGS) performance. The Fragment Analyzer from AATI ensures samples are of suitable quality for further analysis. From FFPE RNA and genomic DNA, to cDNA and small RNA, the Fragment Analyzer delivers reliable assessments of nucleic acid quality when you need them.

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www.aati-us.com

Reduce fatigue when pipetting under a hood

Drummond Scientific

The Drummond Pipet-Aid XL was designed to alter the typical required pipetting motion. The longer, lightweight handle enables the user to rest their elbow on the front edge of the hood counter, shortening the motion required to perform the same pipetting operation as with a conventional pipette. This substantially reduces the strain on the user’s shoulder, arm and hand.

Drummond Scientific

https://ergonomic.expert/

Introducing multi-species kit for toxicokinetic studies

Gyros Protein Technologies

The new Gyrolab Generic TX Kit allows researchers to more efficiently quantify human therapeutic antibodies (IgG) in automated, nanoliter-scale Gyrolab xP and Gyrolab Pore systems. The Gyrolab Generic TX kit complements the Gyrolab Generic Pharmacokinetic (PK) Kit, introduced earlier in 2017, which is based on the same reagents. The TK Kit addresses a higher concentration range compared to the PK Kit, making it more suited to toxicokinetic studies.

Gyros Protein Technologies

www.gyrosproteintechnologies.com


BioVision’s Phosphatidylethanolamine Assay Kit (Fluorometric)

BioVision Inc

BioVision is pleased to launch Phosphatidylethanolamine Assay Kit (Fluorometric) K980 to detect Phosphatidylethanolamine amount in biological samples. BioVision’s kit is a microplate-based enzymatic assay for the quantitation of PE in cells and tissues, and a convenient and non-ELISA alternative to detect phosphatidylethanolamine amount in biological research samples. This assay has advantage of detecting other phospholipids (e.g. phosphatidylcholine, phosphatidylinositol or phosphoric acid), making the kit highly specific. This assay kit can detect as low as 0.2 nmol per well.

BioVision Inc

www.BioVision.com

High-throughput mAb characterization

Carterra

The Carterra LSA is a fully integrated antibody characterization platform that uses Array SPR to analyze up to 384 binding interactions simultaneously, delivering 10 times to 100 times the data in 10 percent of the time with 1 percent of the sample requirements compared to other systems. Combined with our application-focused analytical software, the LSA facilitates kinetic screening, epitope binning, epitope mapping and quantitation.

Carterra

https://carterra-bio.com/

Introducing new BIOSTAT STR bioreactor range

Sartorius Stedim

This new bioreactor range, featuring upgraded hardware and software— as well as a fully integrated, new design of HXsafe 31H single-use bags—ensures quick and easy bioprocess scale-up of biologies and vaccines. The BIOSTAT STR bioreactors are equipped with an improved stainless steel bag holder for user-friendly installation of the single-use flexible STR bag. The bioreactor series consists of five systems in different sizes offers working volumes from 12.5 L to 2,000 L. Because the bioreactors are designed with the same geometries as SBS’s ambr 250 mini bioreactor, the industry gold standard for scale-down, linear scale-up and process transfer from 250 mL to 2,000 L can be achieved in weeks rather than months using this innovative technology platform.

Sartorius Stedim

www.sartorius.com/biostat-str

BioVision’s index

Advanced Analytical.............................................27
www.aaic.org

Advanced Cell Diagnostics, Inc...................................41
www.acdbio.com

American Association Cancer Research (AACR)...........39
www.aacr.org

Beckman Coulter International..................................9
www.beckmancoulter.com

Bio-vid............................................................48
www.bio-vid.com

BioLegend..........................................................3
www.biolegend.com

Bio-Rad Laboratories, Inc.......................................5
www.bio-rad.com

BMG LABTECH GmbH.............................................33
www.bmglabtech.com

Cambridge Healthtech Institute..................................53
www.healthtech.com

Cellbeta, Inc..........................................................29
www.cellbeta.com

Drummond Scientific............................................55
www.drummondsci.com

Essen Bioscience, Inc..............................................34
www.esenbioscience.com

Horizon Discovery Ltd.............................................17
www.horizondiscovery.com

INTEGRA Biosciences AG.......................................47
www.integraproducts.com

IntelliCy, A Sartorius Company..................................43
www.intelliCy.com

ISSCR.................................................................57
www.iscrr.org

Lonza.................................................................2
www.lonza.com

MilliPoreSigma Corporation.....................................11
www.millipore.com/Auanti

New England Biolabs.............................................31
www.neb.com

Origen Technologies, Inc........................................2
www.origene.com

PerkinElmer Corporation........................................2
www.perkinelmer.com

Quanterix Corporation............................................64
www.quanterix.com

R&D Systems, Inc..................................................15
www.rndsystems.com

SternCell Technologies, Inc......................................42
www.sterncell.com

Taconic Biosciences..............................................51
www.taconic.com

The Jackson Laboratory.........................................20-21
www.jax.org

TT Labtech's dragonfly discovery liquid-handling technology

TT Labtech

This liquid-handling technology has been developed to provide researchers with a standard platform whereby they can easily develop complex assays and screen them in a robust and cost-efficient manner. The platform enables rapid and reliable low-volume dispensing and aspiration of multiple disposables in a 96- and 384- and 1,036-well capability. The combination of innovative technology and the incorporation of specific hardware and software features requested by collaborators ensures that dragonfly discovery not only significantly reduces assay development time, but enables more seamless transition from assay development to in the screening phase.

TT Labtech

www.ttlttech.com
TAZ TACKLES GENITAL PSORIASIS

EDINBURGH — Eli Lilly and Co. announced recently that patients with moderate-to-severe genital psoriasis treated with Taltz (ixekizumab) reported a greater decrease in the impact of their condition on sexual activity compared to placebo after 12 weeks of treatment. Results from the Phase 3 trial were presented in an oral presentation at the annual meeting of the American Academy of Dermatology, which took place Feb. 16-20 in San Diego.

“The course of their disease, up to 65 percent of psoriasis patients experience genital psoriasis, which can be difficult to treat and can have a significant impact on their sexual health,” commented Dr. Lotus Mallbris, a vice president and immunology platform team leader at Lilly.

In the study, 149 patients with moderate-to-severe genital psoriasis were randomized to receive Taltz (80 mg every two weeks, following a 160-mg starting dose) or placebo. The impact of genital psoriasis on sexual activity was measured at 12 weeks by pre-specified patient-reported outcomes, including the Genital Psoriasis Sexual Impact Scale, which is composed of the Sexual Activity Avoidance and the Impact of Sexual Activity on Genital Psoriasis Symptoms subscales. Patient-reported outcomes were also measured by the Sexual Frequency Questionnaire item 2, evaluating the impact of genital psoriasis on the frequency of sexual activity, and the Dermatology Life Quality Index item 9, evaluating the impact of skin symptoms on sexual difficulties.

Taltz was superior to placebo as early as week one in terms of the limitations on frequency of sexual activity due to genital psoriasis and as early as week two for the sexual difficulties caused by skin symptoms.

Eli Lilly’s Taltz was first approved by the FDA in March 2016 for moderate-to-severe plaque psoriasis and later in December 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In March 2018, the FDA approved Taltz for the treatment of adult patients with moderate-to-severe plaque psoriasis.

Scientists deliver high-res glimpse of enzyme structure

CAMBRIDGE, Mass.—Using a state-of-the-art type of electron microscopy, a Massachusetts Institute of Technology (MIT)-led team has discovered the structure of an enzyme that is crucial for maintaining an adequate supply of DNA building blocks in human cells. Their new structure also reveals the likely mechanism for how cells regulate the enzyme, known as ribonucleotide reductase (RNR). Significantly, the mechanism appears to differ from that of the bacterial enzyme, suggesting that it could be possible to design antibiotics that selectively block the bacterial enzyme.

“People have been trying to figure out whether there is something different enough that you could inhibit bacterial enzymes and not the human version,” said Catherine Drennan, an MIT professor of chemistry and biology and a Howard Hughes Medical Institute Investigator. “By considering these key enzymes and figuring out what are the differences and similarities, we can target something in the bacterial enzyme that could be targeted with small-molecule drugs.”

Drennan is one of the senior authors of the study, which appears in the Feb. 20 issue of the journal eLife. JoAnne Stubbe, the Novartis Professor of Chemistry Emerita at MIT, and Francisco Asturias, an associate professor of biochemistry at the University of Colorado School of Medicine, are also senior authors. The paper’s lead authors are MIT research scientist Edward Brignole and former Scripps Research Institute postdoc Kuang-Lai Tsai, who is now an assistant professor at the University of Texas Houston Medical Center.

The RNR enzyme, which is found in all living cells, converts ribonucleotides (the building blocks of RNA) to deoxyribonucleotides (the building blocks of DNA). Cells must keep a sufficient stockpile of these building blocks, but when they accumulate too many, RNR is shut off by a deoxynucleotide molecule known as dATP. When more deoxyribonucleotides are needed, a related molecule called dGTP binds to RNR and turns it back on.

Most of the researchers’ previous work on RNR structure has focused on the version found in E. coli. For those studies, they used X-ray crystallography. In the new study, Drennan and her colleagues set out to examine the human version of RNR. This protein’s structure, which turned out to be very different from the bacterial version, proved elusive using X-ray crystallography, which doesn’t work well for proteins that don’t readily crystallize. Instead, the researchers turned to cryogenic electron microscopy (cryo-EM).

Scientists already knew that RNR consists of two protein subunits known as alpha and beta. Using cryo-EM, the


**NEWS**

MIT team found that the human version of the enzyme forms a ring made from six of the alpha subunits. When ATP, which activates RNR, is bound to the enzyme, the ring is unsteady and can be easily opened up, allowing the beta subunit to make its way into the ring. This joining of alpha and beta allows the enzyme’s active site, located in the beta subunit, to perform the chemical reactions necessary to produce deoxynucleotides. However, when the inhibitor GTP is present, the ring becomes much more rigid and does not allow the beta subunit to enter. This prevents the enzyme from catalyzing the production of deoxynucleotides. Several cancer drugs now in use or in development target the human version of RNR, interfering with cancer cells’ ability to replicate. The bacterial version of RNR, involved in the synthesis of rigid six-unit alpha rings.

This six-unit ring is not found in the bacterial form of RNR, which instead assembles into a distinct ring containing four alpha subunits and four beta subunits. This means it could be possible to design antibiotics that target the bacterial version but not the human version. Drennan said. She now plans to investigate the structures of other protein molecules that are difficult to study with X-ray crystallography, including proteins with iron sulfur clusters, which are found in many metabolic pathways.

“The technological advances that have allowed cryo-EM to get to such a high resolution are really exciting,” Drennan said. “It’s really starting to revolutionize the study of biology.”

**More than $4.6M in R&D funds for TB and malaria**

PLYMOUTH MEETING, Pa.—Inovio Pharmaceuticals Inc. announced recently that it is collaborating with The Wistar Institute to advance two novel DNA vaccine programs targeting tuberculosis (TB) and malaria, fully funded by more than $4.6 million in total grants from the Bill & Melinda Gates Foundation and the National Institutes of Health (NIH). Grants from the Gates Foundation (for malaria) and from the National Institute of Allergy & Infectious Diseases (for TB) will fully support Inovio’s efforts to develop new DNA vaccines employing its versatile delivery platform, InovioDYNvelop, which is being tested in rabbits infected with currently approved drugs,” said Dr. Scott M. Hammer, the Harold C. Simmons Professor and Chairman of Surgery at UT Southwestern and the lead investigator of the human clinical trials led by Dr. Drennan and colleagues.

**The record $3.6-billion deal between Nektar (pictured here) and Bristol-Myers Squibb (BMS) announced a record-breaking partnership deal worth up to $3.6 billion involving Nektar’s NKTR-214, a first-in-class compound, in fibrosis diseases. The company said that all PD-1/PD-L1 drugs have identical efficacy and safety when being questioned as clinical data across tumor types mature—will it be interesting to see if the results of these parallel combination trials will be used in a surrogate marker for evaluating the superiority of PD-1/PD-L1 drugs in a particular indication.”**

Furthermore, the firm says that the high volume of partnerships established between early-stage IO companies and established players is evidence of the frenetic pace of deal-making that is occurring in the IO space, concluding: “With this approach of undertaking multiple partnerships, established players can hedge their bets as they wait for more clinical data to become available. However ... BMS put a high-stakes bet on epacadostat in melanoma, NSCLC and tryptophan-2,3-dioxygenase (TDO) inhibitor in hepatic fibrosis and autoimmune diseases,” said Dr. Lyne Gagnon, primary author of the paper and Prometic’s vice president of preclinical research and development.

**BMS and Nektar collaboration lays out new path for combo therapy**

LONDON—In mid-February, Nektar Therapeutics and Bristol-Myers Squibb (BMS) announced a record-breaking partnership deal worth up to $3.6 billion involving Nektar’s NKTR-214, an early-stage immuno-oncology (IO) drug designed to stimulate the expansion of T cells. Under the terms of the agreement, BMS will have an exclusive development period to investigate combination regimens of NKTR-214 and its own in-house pipeline IO drugs Opdivo (nivolumab) and Yervoy (ipilimumab) in 20 indications, notes data and analysis firm GlobalData, which adds: “The ambitious planned development program will span nine tumor types, including non-small cell lung cancer (NSCLC), melanoma, bladder cancer and breast cancer. The majority of these solid tumors represent high competitive markets, with multiple programmed cell death protein 1 (PD-1)-programmed death-ligand 1 (PD-L1) drugs approved for the same indications.”

As companies begin to exhaust the possibility of label expansion for mono-therapy applications of their PD-1/PD-L1 drugs, they have increasingly started exploring the use of combination candidates that could boost the clinical efficacy of their drugs and increase the potential for further approvals, according to GlobalData.

“With the five already-marketed PD-1/PD-L1 drugs and more coming down the pipeline, this creates a competitive scenario in which companies with early-stage IO drugs could find themselves with multiple PD-1/PD-L1 development partners in the same indication,” the firm explained. “Thus far, these partnerships have been largely non-exclusive. Incyte has partnered with both BMS and Merck & Co. to evaluate Opdivo and Keytruda (pembrolizumab), respectively, in sepa-

**The record $3.6-billion deal between Nektar (pictured here) and Bristol-Myers Squibb involving Nektar’s NKTR-214 might spur similar deals by other major pharma players.**

However, the inhibitor GTP, if present, the ring is unstable and can be easily denatured until now. “With the five already-marketed PD-1/PD-L1 drugs and more coming down the pipeline, this creates a competitive scenario in which companies with early-stage IO drugs could find themselves with multiple PD-1/PD-L1 development partners in the same indication,” the firm explained. “Thus far, these partnerships have been largely non-exclusive. Incyte has partnered with both BMS and Merck & Co. to evaluate Opdivo and Keytruda (pembrolizumab), respectively, in separate trials to data become available. In melanoma, Incyte has both ongo-

**PRO 140 for HIV meets primary endpoint**

VANCOUVER, Wash.—CytoDyn Inc. has reported the successful achievement of its primary endpoint in its CD02 Phase 2b pivotal clinical trial with PRO 140 in combination with existing antiretroviral therapy in patients failing their current HIV therapy. The trial data show a sta-

**These data clearly demonstrate the anti-HIV-1 activity of PRO 140 in anti- retroviral treatment-experienced individu-

als who were documented to have ongoing virus replication in the face of therapy with currently approved drugs,” said Dr. Scott M. Hammer, the Harold C. Simmons Professor and chairman of the Division of Infectious Diseases at Columbia University Medical Center/New York-Presbyterian Hospital. “Antiviral drug resistance is an increasing threat to HIV-1 infected persons. Despite the dramatic progress in treatment success over the course of the epidemic, we cannot be complacent. The rapid emergence of drug resistance is a real threat to the prospects of future treatment options.**

**Late-breaking news**

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