A DELUGE OF DATA

Past quarter saw Boehringer Ingelheim release results for multiple trials in pulmonary, oncology areas

BY KELSEY KAUSTINEN

RIDGEFIELD, Conn.—The last few months have been busy ones for Boehringer Ingelheim, as it has had results and analyses to share for several of its ongoing clinical trials. The bulk of the news has come from the company’s efforts in pulmonary diseases and conditions—including asthma, idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD)—but the pharma giant has also had progress to tout in its cancer-fighting efforts as well.

At this year’s CHEST meeting, the company presented a pair of post-hoc pooled analyses of the Phase 3 INPULSIS trials that offered additional support for the efficacy of Ofev (nintedanib) in a variety of people with IPF, regardless of disease severity at the beginning of the trials. INPULSIS-1 and -2 are two identical Phase 3 trials focused on the safety and efficacy of Ofev in treating IPF. The drug received U.S. Food and Drug Administration approval for the treatment of IPF on Oct. 15, 2014, and is the only kinase inhibitor approved for treating IPF.

“Understanding how treatment will affect disease progression for patients who begin drug therapy at different severity levels is critical to helping pulmonologists make treatment decisions,” said Luca Richeldi, professor of respiratory medicine at the University of Southampton in the United Kingdom. “Both of these analyses demonstrated a consistent clinical effect with Ofev in patients irrespective of the severity of IPF.”

Boehringer Ingelheim’s cancer R&D efforts have included a focus on team-ups lately, one of them being that it is joining The Leukemia & Lymphoma Society in a first-of-its-kind collaborative trial program to advance treatments for acute myeloid leukemia.

“Some of us had recently read the book ‘Moneyball,’ an account of how old numbers analysis called sabermetrics, made popular by the film ‘Moneyball.’ Inspired by this moneyball approach, the study “A Data-Driven Approach to Predicting Successes and Failures of Clinical Trials,” published in Cell Chemical Biology, has gone beyond conventional wisdom in pharmaceutical research to develop an objective, machine-learning program called ProCTOR to predict drug toxicity in humans.

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‘Moneyball’ approach may help predict new drug toxicity in humans

BY MEL J. YEATES

NEW YORK—Winning sports teams have long inspired business leaders, but now their strategies are influencing pharmaceutical researchers. The Oakland A’s upended baseball recruiting in 2002 by forgoing conventional wisdom for an objective numbers analysis called sabermetrics, made popular by the film ‘Moneyball.’ Inspired by this moneyball approach, the study “A Data-Driven Approach to Predicting Successes and Failures of Clinical Trials,” published in Cell Chemical Biology, has gone beyond conventional wisdom in pharmaceutical research to develop an objective, machine-learning program called ProCTOR to predict drug toxicity in humans.

Recent findings could lead to new treatments of Rett syndrome and other X-linked chromosomal female diseases

BY DON NEWS STAFF

NEW YORK—The addition of a chemical tag on an RNA molecule is the critical switch that inactivates one X chromosome in every cell, ensuring healthy development in all female mammals, according to new research by Weill Cornell Medicine investigators. The findings, reported in Nature, could offer researchers a new scientific avenue to pursue treatments for X-linked chromosomal diseases in females, such as Rett syndrome.

All cells in female mammals contain two X chromosomes, but only one is needed for proper cell function and development. Weill Cornell notes. In order to ensure the proper expression level of genes on the X chromosome, one of the chromosomes is randomly inactivated every cell in a female mammal. This occurs during embryonic development; once an X chromosome is inactivated, it stays inactive throughout the lifetime of the organism.

The process of X chromosome inactivation is triggered by an RNA called XIST. XIST is a long RNA that attaches to the X chromosome to initiate X inactivation. The Weill Cornell Medicine investigators demonstrated that XIST is not alone empowered to turn off an X chromosome in every cell of a female mammal. Rather, XIST is activated once a chemical tag, called a methyl group, is added all along the length of the RNA. The addition of methyl groups enables XIST to function to inactivate the X chromosome.

“XIST attaches itself at different points all along the X chromosome, silencing the genes that are located on the X chromosome,” said senior author Dr. Samie Jaffrey, a professor of pharmacology at Weill Cornell Medicine. “But exactly how the XIST RNA is capable of silencing genes has been a puzzle. Our study found that XIST is not functional until methyl groups are attached. These act as docking sites to recruit proteins that initiate a cascade of events leading to X chromosome inactivation.”

Researchers at Weill Cornell Medicine in New York recently applied the “moneyball” approach that first gained traction in baseball recruiting in an effort to help predict the outcome of clinical trials.

Researchers at Weill Cornell Medicine in New York recently applied the “moneyball” approach that first gained traction in baseball recruiting in an effort to help predict the outcome of clinical trials.

Chemical tags on RNA silence female X chromosome
From assay to analysis to service and support, this is cell signaling that gets stimulating results.

So where are the breakthrough discoveries in cell signaling coming from? From labs that maximize high-quality results while minimizing hassles, and take an orthogonal approach to glean more biologically relevant information. And we enable those breakthroughs, with complete assay solutions: Innovative technologies such as DELFIA®, LANCE®E, Alpha, AlphaScreen® SureFire, and radiometric assays, with more coming every day. And a range of highly reliable, high-performance multimode plate readers, such as the EnVision® and EnSight™ systems, for a wide choice of detection technologies. It's everything you need to bring about the next big breakthrough. Get the signal?

For more information visit www.perkinelmer.com/cellsignaling
A year-end look to the future of the markets from GlobalData

LONDON—We thought we’d take the end of the year as a nice time to prognosticate, courtesy of some recent (late-October and November) reports from research and consulting firm GlobalData on various pharma and biotech market segments.

Lung cancer

The non-small cell lung cancer (NSCLC) market across the eight major markets (8MM) of the United States, France, Germany, Italy, Spain, the United Kingdom, Japan and China is set to rise from $61.4 billion in 2015 to $26.71 billion by 2025, representing a very strong compound annual growth rate (CAGR) of 15.7 percent, according to GlobalData.

The company’s latest report states that the impressive strength of the market over the next decade can be attributed to the increasing incorporation of premium-priced immune checkpoint inhibitors into the NSCLC treatment algorithm, the launch of new targeted therapies and the rising incidence of the disease across the 8MM.

“In 2015, the NSCLC space was largely dominated by generic chemotherapy and targeted therapies, which accounted for around 94 percent of the market, while immuno-oncology sales accounted for just 6 percent,” noted Dr. Cai Xuan, a GlobalData analyst covering oncology.

“In 2025, the trend will be reversed, with 65 percent of the total NSCLC market going to immuno-oncology therapies and the remaining 35 percent being split between chemotherapy and targeted agents.”

A major trend in corporate strategy is the pairing of programmed cell death protein 1 (PD-1) checkpoint inhibitors with other agents.

Xuan pointed out, adding, “In the crowded PD-1 space, as drugs with identical mechanisms of action are launched, players are looking for ways to boost efficacy in hopes of differentiating their product from that of their competitors.”

In the targeted therapy arena, companies are developing novel therapies for previously unactionable mutations to address high unmet need in specific patient populations. For example, Kirsten rat sarcoma virus (KRAS)-mutant NSCLC makes up a significant (25 to 30 percent) share of the total NSCLC patient pool, yet there are no targeted therapies currently marketed for this segment of the population.

Xuan noted: “Eli Lilly’s pipeline agent abemaciclib targets KRAS patients, yet its lack of efficacy is expected to severely limit its uptake, leaving opportunities for other KRAS-targeted therapies to enter the space.”

“In addition to novel therapies, companies are also developing second- and third-generation targeted therapies to provide better options for patients with actionable mutations. GlobalData expects these next-generation targeted therapies to take significant patient share away from their predecessors.”

Arthritis

The psoriatic arthritis market across the seven major markets (7MM) of the United States, France, Germany, Italy, Spain, the United Kingdom and Japan is set to grow from $4.5 billion in 2015 to around $12.6 billion by 2025, representing a CAGR of 10.74 percent.

GlobalData’s latest report on this market states that the relatively strong growth will primarily be driven by the increase in diagnosed prevalent cases. The launches of interleukin (IL)-17 inhibitors, such as Eli Lilly’s Taltz (ixekizumab) and AstraZeneca’s Lumicef (brodalumab), as well as Celgene’s oral therapy Otezla (apremilast), will also drive the market.

“Reasons for the increased diagnosed cases of psoriatic arthritis include better awareness of the disease due to educational campaigns and an interdisciplinary approach to managing the condition between dermatologists and rheumatologists,” said Alexander Annis, a GlobalData analyst covering immunology.

“As such, the number of total treated cases in the 7MM is expected to increase from around 770,000 in 2015 to almost 1.2 million by 2025.”

The psoriatic arthritis community has welcomed the recent approval of Novartis’ IL-17 inhibitor Cosentyx, which touts the highest clinical efficacy of any biologic yet approved. X-ray assessment data has demonstrated that 84 percent of patients showed no further progression of structural joint damage over two years of Cosentyz.

Annis continued: “The psoriatic arthritis market will be full of therapeutic options, with nine branded biologic drugs on the market over the forecast period. This includes the recent approvals of Lumicef and Taltz in Japan, as well as an oral system. Otezla, and three new biologic and oral drugs in the late-stage pipeline.”

GlobalData expects most of the current pipeline products will be launched by mid-forecast, with Lumicef and Taltz leading the way. In 2025, with all of the approved drugs trying to jockey for position and stand out among the rest, Taltz will gross an estimated $1.42 billion in total drug sales—the highest among IL-17 inhibitors. Overall, a crowded treatment space and a constant need for reduced drug costs mean new entrants will find it difficult to make an impact on the psoriatic arthritis therapy space.

Influenza

The seasonal influenza vaccine market across the 8MM is expected to increase from $3.13 billion in 2015 to $4.35 billion by 2025, at a CAGR of 3.5 percent, GlobalData maintains in a recent report. The main growth drivers during the forecast period will include amendments to the national immunization schedules of the United States and United Kingdom; the expansion of egg based quadrivalent seasonal influenza vaccines across Germany, Italy, France and Spain; and the transition from egg-based to cell culture-based vaccines.

“For the past few decades, children have not been the focus of season influenza immunization recommendations in developed nations,” noted GlobalData’s director of infectious diseases, Dr. Christopher J. Pace. “More recently, developed countries such as the U.S. and the U.K. have issued expanded recommendations for the vaccination of healthy children and adolescents against seasonal influenza, thereby indirectly protecting high-risk groups such as the elderly and the immunocompromised from disease by disrupting community transmission. This generates a significant new opportunity for manufacturers.”

Quadrivalent influenza vaccines, which contain antigens against two influenza type A and two influenza type B subtypes, offer broader cover- age than trivalent (two influenza A and a single influenza B strain) formulations. In 2015, Japan replaced its trivalent, seasonal influenza vaccines with quadrivalent formulations, and it is expected that trivalent vaccines will be virtually absent from the U.S. market within the next five years. Quadrivalent vaccines will also expand throughout Europe by 2025.

Pace continued: “Although the vaccination rate across the 7MM is anticipated to remain stable during the next decade, the higher price commanded by quadrivalent vaccines and other next-generation immunizations, such as Fluzone High-Dose and CSL Limited’s Fluaad, is expected to drive market growth.”

With regard to the transition from egg-based to cell culture-based vaccines, 2016 saw CSL Limited launch the first quadrivalent cell culture-based vaccine on the U.S. market indicated for the immunization of children over 4 years old—Flucelvax. GlobalData noted that its novel manufacturing platform, which produces a significantly higher production compared to egg-based vaccine production and also can be administered to individuals who have egg allergies, giving cell culture-based vaccines an important edge in an intensely competitive marketplace.

“Novavax’s and Mitsubishi Tanabe’s novel virus-like particle vaccines are also anticipated to further revitalize an influenza market that is gradually moving towards the eventual development of a universal seasonal influenza vaccine,” Pace added.

PCR industry likely to see consistent growth through 2021

WELLESLEY, Mass.—In BCC Research’s recent report, “Polymerase Chain Reaction (PCR) Technologies and Global Markets,” the firm forecasts a five-year compound annual growth rate (CAGR) of 4.4 percent from 2016-2021, leading to a global market size of $9.8 billion in the end year of that range.

Market drivers include advancements in instrumentation, reagents and PCR techniques, increased R&D efforts, the growing incidence of diseases and an aging population.

Rising product sales from U.S. companies, growing improvements of disease diagnosis and expanding healthcare in emerging markets are keying growth as well.

As BCC Research notes, PCR allows DNA sequencing as well as the production of millions of copies of a specific DNA sequence within minutes. PCR technologies are widely used in many areas, including R&D, clinical domain and other applications. DNA cloning and sequencing, gene expression, genotyping, forensic science, bioinformatics, disease diagnosis, tissue typing and blood screening are some of the domains where PCR technologies are frequently used.

PCR has become a popular clinical molecular diagnostic method due to its ability to make early diagnoses, because it takes less time to perform the test and generate the result.

The new report explores the current and future PCR product market, which includes instruments, reagents and consumables, software and services. The report looks at innovations, market drivers and forces holding back the market. In this analysis of the PCR market, product inspections are broken down by region and sales figures are estimated for the five-year period from 2016 through 2021. Applications and technologies of various PCR technologies are also discussed. The report also covers significant patents related to PCR technology.

PCR companies’ acquisition strategies and collaborations are also covered in this report. This study also discusses the strengths and weaknesses of many PCR companies and new technologies, growing competition and changing customer needs.

The scope of the study was global, and the geographical regions covered include the United States, Europe and emerging markets such as India, China, Japan, Korea, Taiwan, Africa, Australia, New Zealand and Canada. «
Sofinnova raises $650M for biotech-focused venture fund

MENLO PARK, Calif.—Sofinnova, a biotech-focused investment firm, announced in October the closing of Sofinnova Venture Partners X at its hard cap of $650 million. The initial fund target was $550 million.

Sofinnova was founded in 1974 and has offices in San Diego in addition to Menlo Park. Since 2007, and the launch of Sofinnova Venture Partners VII, the Firm has focused on biopharmaceuticals and specialized in clinical-stage investments. The three general partners for Fund X have worked together since 2007. Sofinnova Venture Partners Fund X is the fourth fund to follow the focused strategy of investing primarily in mid- and later-stage investments.

Over the past decade, Sofinnova has raised roughly $2 billion to invest in biotechnology companies that are developing drugs that address high unmet medical needs and improve the lives of patients. The capital for Fund X was raised from existing and a select group of new institutional investors.

“We are grateful for the tremendous support of our investors during this fundraising,” said Jim Healy, Sofinnova general partner. “We appreciate the significant ongoing commitment of our existing investors and have the privilege to add a small number of new highly esteemed institutional investors.”

Fund X will seek to invest in 20 to 25 companies, with amounts typically ranging from $15 million to $35 million per company. Since 2007, Sofinnova has invested in 46 companies in the areas of rare and orphan diseases, oncology, women’s health, dermatology, ophthalmology and infectious diseases.

CPhI Korea notes trend toward increased pharma exports and nutraceuticals

SEOUL, South Korea—During the 2016 CPhI Korea conference hosted by UBM EMEA and co-organized with the UBM Korea Corporation and Korean Pharmaceutical Traders Association, one of the key trends that emerged was a notable increase in globalization. Highlighting this major shift, CPhI Korea 2016 saw a 38 percent increase in overseas attendees, with sessions exploring market-entry strategies for the European Union, Japan and China.

Among the highlights noted at CPhI Korea:

First, the Korean government is actively working to attract foreign investment. The launch of the $150 million Global Healthcare Fund, co-organized with the UBM Korea Corporation, is a notable example. The fund is expected to reach $1.2 billion by 2019.

Second, the Korean biosimilar market is rapidly growing, reaching $1.7 billion. Mirroring this growth, the CPhI Korea device market has seen a steady growth in recent years.

Finally, the Korean nutraceutical sector has undergone a significant change in the last year, reaching $1.5 billion. Building on this success, the CPhI Korea opened its first-ever Health Ingredients Korea event co-located with CPhI.

“It has been fantastic to see Korea’s rapid progression in the three years that we have hosted CPhI Korea,” said Rutger Oudejans, brand director for pharma at UBM EMEA. “It has seen growth not only in terms of overall production levels, but also moved up the value chain into biosimilars, and more recently nutraceutical sales regionally. Manufacturers in the country are increasingly experiencing a good deal of international activity, highlighted by the growing international audience of the event, with many exporting to nearby economies.”

Rutger Oudejans of UBM EMEA

Neuromodulation devices market set to grow in developing countries

PORTLAND, Ore.—The neuromodulation device market has seen a steady growth in the last decade, notes Snehil Chougule, senior digital marketing executive at Allied Market Research, and the market size has grown, owing to the wide array of medical applications in chronic pain, epilepsy, tremor and migraine. In addition, the rise in geriatric population worldwide has also contributed to this expansion.

As Allied Research makes clear, the technology has been adopted on a larger scale in highly developed regions, such as the United States, Canada and Europe, and the technological advancements and developments in the field of neuromodulation in the aforementioned regions has led to a higher adoption rate. Developing countries such as China and India, however, are gradually embracing new innovations in the field of neuromodulation.

According to Chougule, the true potential of neuromodulation devices “has not been recognized yet as the technology is still at a nascent stage,” but Allied Research has released a report recently with insight into the neuromodulation devices market.

Chougule points in particular to the potential for neuromodulation devices in treating Parkinson’s disease. Neurostimulators are implanted into the brain, and the surgically implanted devices may help to deal with tremors and potentially eliminate them altogether, Chougule says.

New medications and developments have shown promising results in Parkinson’s, but are still in the testing phase—nilotinib and isradipine are just drugs that have delivered positive results and hold a promising future, Chougule notes. Also, in 2011, DaTscan, a radiopharmaceutical agent, got FDA approval and may be useful in Parkinson’s care. The rise of these and other therapeutics and diagnostic advances, Chougule maintains, is further driving the neuromodulation device market. 
**Endometriosis**

The endometriosis market across the 7MM is set to rise from around $1.72 billion in 2015 to just over $2 billion by 2025, representing a CAGR of 1.7 percent. This modest growth is driven by increased disease awareness and earlier diagnoses, improvements in non-invasive diagnostic methods and, most importantly, the launch of elagolix in the United States and Europe 2018.

Dr. Edit Kovalcsik, a GlobalData analyst covering neurology and ophthalmology, “Currently, there are no drugs approved for patients who are refractory or become unresponsive to Jakafi treatment, and momelotinib and imetelstat are expected to contribute towards addressing this issue with launches in the second-line setting in 2017 and 2021, respectively.”

Despite this rising competition from pipeline agents, Jakafi is expected to retain its leading spot in the market, with just over 50 percent of the market share in 2025. GlobalData expects that momelotinib can ultimately only capture about 25 percent of Jakafi’s patient share in the first-line setting.

In Japan, the launch of GnRH antagonist relugolix will have a minimal impact on the endometriosis market. However, the Japanese market will still undergo sustained growth during the forecast period.

**Myelofibrosis**

The myelofibrosis market is expected to almost double in value from $645.2 million in 2015 to $1.02 billion by 2025 in the 7MM, representing a CAGR of 6.4 percent, primarily driven by the launch of pipeline agents, including Gilead’s momelotinib, Promedior’s PRM-151 and John-son & Johnson/Geron’s imetelstat. Other factors include an increase in the incidence of myelofibrosis and a rise in the use of drugs for the treatment of splenomegaly and constitutional symptoms.

“Incyte/Novartis’ Jakafi is currently the only drug approved for the treatment of myelofibrosis-associated splenomegaly and constitutional symptoms in the 7MM,” explained Dr. James Beggs, a GlobalData analyst covering oncology and hematology. “Currently, there are no drugs approved for patients who are refractory or become unresponsive to Jakafi treatment, and momelotinib and imetelstat are expected to contribute towards addressing this issue with launches in the second-line setting in 2017 and 2021, respectively.”

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“Imetelstat, a first-in-class telomerase inhibitor, is expected to struggle for market penetration due to late market entry and the high level of toxicity shown in previous clinical trials. GlobalData estimates sales of the drug in 2025 to be only $21.2 million, representing just 2 percent of the myelofibrosis market in the 7MM,” Beggs said. “PRM-151, however, looks more promising in terms of expected sales.”
Cloud Pharmaceuticals looks to the crowd

RESEARCH TRIANGLE PARK, N.C.—Cloud Pharmaceuticals Inc. is going to the people with a crowdfunding effort to finance orphan drug development for amyotrophic lateral sclerosis and Zika. The company hopes to fast-track its efforts with its rapid discovery platform, which combines artificial intelligence, cloud computing and molecular modeling to design new drugs. Should its efforts prove successful, Cloud intends to continue compound design and develop the compounds itself or with partners.

“The diseases affect a relatively small percentage of the population, so there is less incentive for pharmaceutical companies to invest in efforts to treat or prevent the diseases,” said Cloud Pharmaceuticals CEO Ed Addison. “Crowdfunding enables us to fund that work and continue our efforts to improve health and well-being through the computational design and rapid development.”

CD3 announces fund for drug development

LEUVEN, Belgium—In an effort to turn research into reality, the Centre for Drug Design & Discovery (CD3) has established a €60-million fund provided jointly by KU Leuven Research & Development and the European Investment Fund. The new fund will enable CD3 to move drug candidates into clinical development on its own and together with industrial partners. CD3 works to provide expert drug discovery capabilities and financial means to academic research groups and small companies to discover innovative small-molecule drugs.

“With this new fund, we can now build on our initial successes and further dig into new unexplored avenues for the discovery of new medicines that address some of the most serious medical needs of our time,” remarked Dr. Patrick Chauvin, managing director of CD3.

BRIEFS

Cloud Pharmaceuticals looks to the crowd

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As simple as ADC

Scripps Research Institute explored the protein IP6K1 as a potential therapeutic approach for obesity and diabetes.

Growing interest in IP6K1

TSRI studies show the protein is a promising target for treating obesity, diabetes.

BY KELSEY KAUSTINEN
JUPITER, Fla.—The U.S. Centers for Disease Control and Prevention estimate that as of 2014, 29.1 million people—9.3 percent of the population—had diabetes, and obesity rates for children and adults are at 17 and 36 percent, respectively. As those numbers continue to climb, the search continues for therapeutic approaches to help patients manage their weight and insulin levels.

And in the midst of that research, a new target has emerged. The protein in question, IP6K1, was examined in a trio of studies led by Dr. Anutosh Chakraborty, an assistant professor at the Florida campus of The Scripps Research Institute (TSRI), and the results were published in The International Journal of Biochemistry & Cell Biology, Molecular Metabolism and The Journal of Clinical Investigation.

“The ubiquitously expressed enzyme IP6K1 primarily generates the signaling ‘inositol pyrophosphates’ in the body. Inositol pyrophosphates bind or pyrophosphorylate their target proteins. IP6K1 also regulates some other proteins by direct binding. As a result, IP6K1 regulates various cellular processes including energy metabolism. IP6K1 promotes energy accumulation, especially in fat cells,” explains Chakraborty. “Moreover, IP6K1 reduces insulin’s efficacy in high-fat-fed mice. Therefore, IP6K1 CONTINUED ON PAGE 7

New findings about cytomegalovirus

Research into CPEB1 protein may offer hope for new therapies to fight CMV infection.

BY RACHEL FLEHINGER
SAN DIEGO—Researchers at the University of California, San Diego (UC San Diego) School of Medicine have uncovered a link between cytomegalovirus and the human protein CPEB1, which could offer new hope for CMV therapies. Pictured here is UC San Diego’s Leichtag Biomedical Research Building.

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X-linked diseases

Chemical tags on RNA silence female X chromosome (SILENCE from cover)

As simple as ADC

Swiss-based NBE and Czech Republic’s SOTIO sign license deal for next-gen ADCs in oncology

BY LORI LESKO
BASEL, Switzerland—Targeted toward discovering more efficient ways to treat cancer, privately owned bio-tech NBE Therapeutics AG and Prague, Czech Republic-based SOTIO have entered into a collaboration and license agreement for the development of next-generation antibody-drug conjugates (ADCs) for improved cancer therapy. Both companies have declined to disclose financial details of the collaboration.

With agreement, NBE seeks to become a leader in antibody-based therapies by developing its own portfolio of drugs to the point of demonstrating clinical proof of concept in man. SOTIO ADC CONTINUED ON PAGE 3
mice with global or fat cell-specific deletion of IP6K1 are protected from diet-induced obesity (DIO), insulin resistance and fatty liver. Accordingly, the IP6K inhibitor TNP [N2-(m-Trifluorobenzyl), N6-(p-nitrobenzyl)purine] protects mice from these metabolic aberrations. In addition, the compound promotes weight loss and restores insulin sensitivity, when dosed to mice that are already DIO.

Given these results, some of the greatest interest related to IP6K1 is in blocking it with inhibitors such as TNP. Energy expenditure—specifically fat energy—follows the process of lipolysis, which breaks down stored fat or triglycerides into free fatty acids and glycerol for cells to use as energy. When IP6K1 is deleted, it affects its interaction with another protein and enhances the breakdown of fats. When IP6K1 was deleted in the fat cells of animal models, the animals saw enhanced energy expenditure as well as protection from DIO and insulin resistance.

“IP6K1 reduces insulin’s efficacy in high-fat-fed mice. Therefore, mice with global or fat cell-specific deletion of IP6K1 are protected from diet-induced obesity, insulin resistance and fatty liver.”

Anutosh Chakraborty of The Scripps Research Institute

is deleted, it affects its interaction with another protein and enhances the breakdown of fats. When IP6K1 was deleted in the fat cells of animal models, the animals saw enhanced energy expenditure as well as protection from DIO and insulin resistance.

“In addition, the compound facilitates weight loss and improves metabolic parameters when used in animals that are already obese,” Chakraborty noted in a press release.

Despite its promise, however, Chakraborty admits TNP “has several shortcomings,” and as such, “research is ongoing to overcome these obstacles, which will generate novel IP6K inhibitors with higher efficacy and minimum side effects. Testing these compounds in rodents and higher primates will be the next step.”

Given its effect on fat breakdown and insulin resistance, it’s unknown whether or not IP6K1’s activity is altered in obese or diabetic individuals, but Chakraborty tells DDNews his lab is working to answer that question.

“As for how the deletion of this protein can protect against insulin resistance, Chakraborty notes that “Protein kinases Akt/PKB and AMPK maintain insulin sensitivity. In addition, AMPK enhances energy expenditure, which reduces energy storage. IP6K1 inhibits Akt and AMPK via distinct mechanisms, which promote insulin resistance and weight gain. Moreover, adipocyte-specific IP6K1-KO mice exhibit increased plasma levels of adiponectin, which is an insulin sensitizing cytokine secreted from the adipose tissue. Therefore, IP6K1 exerts pleiotropic inhibitory effects on the insulin signaling pathway.”

“Obesity is a global epidemic. In the U.S., 34.9 percent of adults are obese, of which 9.3 percent also have type 2 diabetes (T2D). Obesity/T2D leads to various other life-threatening diseases, such as heart diseases, stroke and neurodegeneration. Although lifestyle interventions are effective for weight control, a significant number of patients exhibit inadequate long-term responses. Thus, anti-obesity pharmacotherapy is essential. Unfortunately, current anti-obesity medications are only partly effective. Therefore, new drugs, with long-term efficacy and without substantial side-effects, are urgently needed, especially for patients who are refractory to current treatments,” says Chakraborty.

“IP6K1 reduces insulin’s efficacy in high-fat-fed mice. Therefore, mice with global or fat cell-specific deletion of IP6K1 are protected from diet-induced obesity, insulin resistance and fatty liver.”

Anutosh Chakraborty of The Scripps Research Institute
Ubiquigent launches novel compound library designed to target deubiquitylase enzymes

DUNDEE, U.K.—This fall, Ubiquigen Ltd., a company specializing in providing ubiquitin cell-signaling system drug discovery services and research tools, announced that it had launched what it says is the first commercially available compound library, named DUBTarget-001, comprising novel small molecules designed to target deubiquitylase (DUB) enzymes.

To mark the launch of the library, Dr. John Harris, a member of Ubiquigen’s scientific advisory board, presented DUBTarget-001 at the Society of Chemical Industry conference. Harris, in collaboration with the Drug Discovery Unit (DDU) at the University of Dundee, has jointly developed the library to support both commercial and academic researchers looking to either enter the ubiquitin drug discovery field or to support those with active programs but who are seeking to access additional chemical diversity.

The design of DUBTarget-001 (DDU) at the University of Dundee, has jointly developed the library to support both commercial and academic researchers looking to either enter the ubiquitin drug discovery field or to support those with active programs but who are seeking to access additional chemical diversity. (led by Dr. Andrew Woodland of the DDU) has been informed by DUB-related structural data to yield a library with the potential to have activity across multiple DUB families. Ubiquigen has already screened the library against USPs (a DUB with potential roles in oncology) and demonstrated a significant number of hits from different structural classes. These structures represent multiple starting points with the potential to lead to the development of novel therapeutics.

The library is now available in either its physical form for screening within researchers’ own laboratories or as a dataset where the library will be screened against any of the 40 other DUB enzymes included within Ubiquigen’s DUB-profiled screening platform.

“DUB-targeted libraries are the keys that can unlock the multiple therapeutic opportunities that are emerging for the exploitation of novel DUB inhibitors,” said Ubiquigen’s executive chairman, Dr. Mark Teherner. “DUBTarget-001 is the first of a pipeline of innovative libraries that will link ubiquitin research to new drug discovery opportunities for oncology, neurodegeneration and many other chronic diseases with significant unmet medical need.”

Harris noted: “As has become clear in the kinase inhibitor field, the application of libraries that have been custom-designed with the structure and mechanism of the drug target(s) in mind is expected to be a substantially more effective route to innovative and potent starting-points for DUB candidate drugs than target-agnostic screening approaches.”

CMV CONTINUED FROM PAGE 6

link between CMV and CPEB1: “We found that CPEBs, one of a family of hundreds of RNA-binding proteins in the human genome, is important for establishing productive cytomegalovirus infections,” said senior author Dr. Gene Yeo, professor of cellular and molecular medicine at UC San Diego School of Medicine.

According to the U.S. Centers for Disease Control and Prevention, CMV is a common virus that infects people of all ages. Over half of adults by age 40 have been infected with CMV, and once it is in a person’s body, it stays there for life and cannot be eradicated. Most people infected with CMV show no signs or symptoms. However, CMV infection can cause serious health problems for people with weakened immune systems such as from organ and bone marrow transplants, and people infected with human immunodeficiency virus (HIV), as well as babies infected with the virus before they are born, known as congenital CMV. Yeo’s team discovered that CPEB1 levels increase dramatically in humans cells infected by CMV. Using genomics technologies, the researchers also found that increased CPEB1 levels in CMV-infected cells leads to the abnormal processing of RNAs encoding thousands of human genes. In addition, they were surprised to find that CPEB1 levels increase for years. “enabling the world’s leading brands to achieve sustainable growth,” says Melo, who joined Amyris just months after the company’s initial public offering.

According to Deoras, “We’re excited by how quickly we’ve achieved initial success in this project for one of the largest and most innovative companies in the sector,” said John Melo, Amyris’ president and CEO. “We believe our technology platform is well suited to efficiently drive advancements in drug discovery while meeting our partners’ unique requirements and helping to save lives. Our demonstrated capabilities have led to signing several partnership agreements with leading global pharmaceutical companies this year. We are achieving in months what these companies have been chasing for years.”

Continued Melo, “Along with more than doubling our revenue this year, we are accelerating time to market for our biopharma partners. Our work to replace mammalian cells, deliver better antibiotics and discover new oncology treatments has the potential to transform drug discovery and make more available leading treatments to improve the lives of patients throughout the world.”

Amyris is an integrated renewable products company that is “enabling the world’s leading brands to achieve sustainable growth,” according to the company. Amyris applies its innovative bioscience solutions to convert plant sugars into hydrocarbon molecules and produce specialty ingredients and consumer products. The company reports that it is delivering its No Compromise products across a number of markets, including specialty and performance chemicals, flavors and fragrances, cosmetics ingredients and pharmaceuticals and nutraceuticals.

Amyris achieves key milestone in major drug discovery collaboration

EMERYVILLE, Calif.—Amyris, Inc., an industrial bioscience company, recently announced that just months after initiating a collaboration with one of the world’s leading pharmaceutical companies, it has successfully achieved the first milestone under the agreement. This milestone, the company says, resulted in the creation of a robust, sensitive activity assay for an oncology target in a live yeast strain. This high-throughput assay enables screening for chemical diversity found in nature using Amyris’s proprietary µPharm platform, with the potential to provide previously inaccessible molecule targets.

The µPharm platform combines two powerful technologies that can significantly accelerate and reduce the cost of new drug discovery. The Amyris platform is “groundbreaking,” the company says, in its ability to design and scale molecules that are “becoming disruptive workhorses across several industries.”

This capability is unique, according to Amyris, allowing broad access to a significant variety of naturally evolved molecules in a rapid, high-throughput format. Active molecules can be scaled for production in yeast, further tested and developed into market-ready pharmaceuticals at a cost and speed that the company believes has not been realized before in the pharmaceutical industry.

“We’re excited by how quickly we’ve achieved initial success in this project for one of the largest and most innovative companies in the sector,” said John Melo, Amyris’ president and CEO. “We believe our technology platform is well suited to efficiently drive advancements in drug discovery while meeting our partners’ unique requirements and helping to save lives. Our demonstrated capabilities have led to signing several partnership agreements with leading global pharmaceutical companies this year. We are achieving in months what these companies have been chasing for years.”

Amyris applies its innovative bioscience solutions to convert plant sugars into hydrocarbon molecules and produce specialty ingredients and consumer products. The company reports that it is delivering its No Compromise products across a number of markets, including specialty and performance chemicals, flavors and fragrances, cosmetics ingredients and pharmaceuticals and nutraceuticals.

EDITCONNECT: E121605

The human RNA-binding protein CPEB1 (green) plays an important role in cytomegalovirus (orange) infections.

For more information, visit www.DDN-News.com
SILENCE CONTINUED FROM PAGE 1

Jaffrey and his colleagues demonstrated in a 2012 study that many RNAs in the cell contain methyl modifications. “We found that methyl modification is a normal feature of most RNAs in the cell,” he said. “This includes messenger RNAs that encode proteins, as well as noncoding RNAs such as XIST.”

“We were particularly surprised by the unusually high number of methyl groups in XIST. That seemed very suspicious,” Jaffrey added. “So we wanted to explore what would happen if we took away the ability of the cell to make methyl modifications in XIST.”

The researchers used human and mouse cells to study what would happen if they turned off a cell’s ability to tag XIST with methyl groups. They found that cells that could not methylate XIST were not able to carry out X chromosome inactivation.

“The researchers also found a protein, called DC1, that binds to every methyl group on XIST and enables it suppress the X chromosome. When they removed DC1 from the cells, XIST was unable to turn off the X chromosome.”

“Exactly how the XIST RNA is capable of silencing genes has been a puzzle. Our study found that XIST is not functional until methyl groups are attached. These act as docking sites to recruit proteins that initiate a cascade of events leading to X chromosome inactivation.”

Dr. Samie Jaffrey of Weill Cornell Medicine

ADC CONTINUED FROM PAGE 6

Weill Cornell Medicine researchers have gained insights into the silencing of X chromosomes that could lead to better discovery and development of treatments for X-linked female chromosomal diseases. Picture here is the Weill Cornell Medical College class of 2016 taken in 2012.

“NBE fits to SOTIO’s strategy of expansion in the biotechnology industry,” says Jens Hennecke, chief business officer of SOTIO. “We are building a diverse pipeline of innovative oncology products that could provide more effective and safer treatments for patients with cancer. NBE perfectly fits to it.”

“We will strengthen our capabilities and resources for clinical development of our own ADC pipeline, and SOTIO can profit from our know-how and superior technologies in ADC development and manufacturing.”

“It is NBE’s goal to develop the best ADCs candidates for SOTIO in the shortest possible time,” he adds. “This will add to the validation of our ADC development capabilities.”

According to Grawunder, this agreement “has changed NBE by accelerating the planning for cGMP manufacturing of ADCs and for IND/IMPD enabling preclinical experiments.”

Ladislav Bartonicek, CEO of SOTIO, states, “NBE’s product platform addresses the key issues of today’s antibody-drug conjugates. With the very strong preclinical data generated by NBE that show superiority in terms of potency, safety and product homogeneity—as well as strong immunotherapeutic effects—this platform has the potential to provide new superior treatment options for cancer patients.”

“NBE fits to SOTIO’s strategy of expansion in the biotechnology industry,” echoes Jens Hennecke, chief business officer of SOTIO. “We are building a diverse pipeline of innovative oncology products that could provide more effective and safer treatments for patients with cancer. NBE perfectly fits to it.”

If this collaboration proves a success, the market for the ADC products would be huge globally. SOTIO’s goal “is to finalize preclinical development, choose indications for further clinical development and realize necessary clinical trials to prove safety and efficacy of NBE’s ADC products,” Hennecke says. “If clinical trials are successful, our ultimate target is registration and commercialization of the ADC products.”

Hennecke could not specify which kinds of cancers researchers in this partnership would focus on, saying only that while the focus will be in oncology, “The choice of indication depends on the target and will be data-driven.”

Czech Republic-based SOTIO (pictured here) recently entered into a collaboration and license agreement for the development of next-generation antibody-drug conjugates with Swiss company NBE Therapeutics.

Weill Cornell Medicine
I HAVEN'T OPINED IN MY monthly editorials and my attitude was very “wait and see)” and in May when it was an actual bill to pass in the U.S. Congress (and my attitude was “cautiously optimistic”).

But it’s time to revisit the issue before we get running out of control that the bill got broad bipartisan support in the House of Representatives and passed, but got bogged down in the Senate, then a revamped version just got passed by the House and, just as we went to the printer with this issue, the Senate passed it as well.

My current attitude: Confused and uncertain. Not sure about what’s right or what’s wrong for me right now, so soon after the recent U.S. presidential election. I tend to avoid getting political in my editorials, but let me just say that the expression “May you live in interesting times”—which, while seemingly a blessing, is actually usedironically as a sort of curse/apocryphal expression—would lead many of the United States for at least the next four years.

But as it relates to the 21st Century Cures situation, I am a bit concerned about how this might impact the U.S. Food and Drug Administration. As chief editor of this magazine, I have an emotional and intellectual relationship with the FDA that would, were it a Facebook status, be defined as “it’s complicated.”

On the one hand, the part of me that deals with pharma and biotech business issues knows that it would be nice to trim the costs of clinical trials and other aspects of the approval process. Unlike most of the American population, I know that high drug prices are often at least as much to do with the economics of grouping R&D costs as they are to do with greed.

On the other hand, I also deal with the academic and clinical researcher side of the news and a lot of the people on that side (and me, too) would like to see rigorous scientific study of potential drugs. I was happy in the early talk of 21st Century Cures to hear about working in a “real world” results as part of the review/approval process and possibly streamlining some FDA processes. Given what seems to be from the corpo- rate side and many patient advocacy groups, I have some concern that this bill, should it become law, might actually reduce scientific rigor instead of improving the data, and might undermine the FDA’s ability to accurately assess potential drugs. To see some of these comments and insights (other than mine) with regard to 21st Century Cures, go to page 32 in this issue for the article “Commenting on Cures.”

However, despite those reservations, I am—if nothing else—glad to see that, so far, 21st Century Cures allocates $4.8 billion to the National Institutes of Health that is aimed at funding the Precision Medicine Initiative, the BRAIN Initiative and the Cancer Moonshot initiative.

Let’s hope that, if nothing else, Congress makes sure we have some research funding and doesn’t take away all of the FDA’s teeth. »

THE NEXT BIG THING

THE 21ST CENTURY CURSE ‘IN THE MAKING?’

PETER T. KISSINGER

W E COME TO END of another year and another administra- tion. I’m thinking of change as were many voters in this election year. When I began to play in the global life-sciences business in the 1970s, the telex machine (teletypewriter) was king, an electromechanical wonder that chattered and rattled to call us to attention. Variants of these wondrous devices were popular for punching yellow paper tape programs into mainframe computers. An input/output device of the most primitive sort—it was a mature device in my immaturity, having been introduced in the 50’s.

It was a joy to come to the office each morn- ing and unroll the paper, hoping for orders from Hong Kong or Frankfurt, but please no service problems from Australia. Fax, and then Federal Express, came to the rescue. They were very costly and special, but accommodated graphics and even hand scribbles on hotel station- ery in Bavaria. Within five years or so the bloom fell off and fax machines digested menus from local restaurants, fras from Nigeria and the favorite fraud of all, invoices for fax paper that had never shipped.

The first email brought us back to the telex machine: words without graphics. The signal-to-noise ratio was at first high and very special. They got an email that said, “We just sent you a chromatogram by fax.” Then the pollution increased exponentially with access to the web and bandwidth to accommodate attachments. A decade later we were expected to network socially, although with more noise and jokes than substantive data. Video then fried more neurons and national human productivity sank as robots took over. Now all this is in our pocket. Are we done yet? Can I rest?

These developments have impact- ed science in ambiguous ways. The rise of endless commercial journals and open-access publications that print nothing eats up our time. Much is published in a third (or even fourth tier) that is not well reviewed, and found to be irreproducible. Some even advocate mak- ing preprints widely available with- out review. Transmission costs now approach zero, paper is only used locally, postage is irrelevant and the human brain is not advancing. Could it perhaps be slipping from multitasking under the weight of Big Data? I recall the 1990s when genomics was new, and then proteomics, metabolomics, lipodomics and more. They all were the next big thing. They became easier (to do) and harder (as the unknown unknowns became known).

Today the lower frictions to get data has outstripped the ability to interpret it or even properly repeat it. What to do? Invent complex data sets, hoping that enough of it will result in enlightenment, even with much of the data being junk? Is the microhome getting old too fast? CRISPR too? Optogenetics? But we haven’t finished riding the earlier ‘omics waves which thus far benefit only a few patients. I see parallels with an open- access press. There truth has been sacrificed to the priority of supporting a political narrative. Even worse, it appears the same has happened in science, with so many press releases publicizing biomarkers far from clinical validation and drug targets proven to be either safe or effective (i.e. druggable).

The public press is beginning to wonder about science-by-tweet in parallel with what we see as corruption in drug pricing, config- ration bias in clinical trials and even, in a few cases, creating diseases to fit drugs at hand.

For more information, visit www.DDN-News.com
COMMENTARY: Science of cell culture—Maintaining phenotypic and genotypic heterogeneity

BY DR. MINDY GOLDSBOROUGH, ATCC

CONTINUOUS CELL LINES are most often derived from complex tumor tissues and generally reflect the heterogeneity of the original tumor. With the adoption of analytical methods that enable researchers to explore tumors at the single-cell level, it has become clear that many tumors are quite heterogeneous due to both genetic and non-genetic variability. For most studies, upholding the tumor heterogeneity in culture is important as it best reflects the tissue of origin. When cell lines are established, a snapshot of the composition of the original tumor that may not reflect the heterogeneity across laboratories. Through periodic testing and translational research applications, the various phenotypes and genotypes can be identified before publication of results or across laboratories. Monitoring the markers that are unique to the original tissue is therefore critical.

Maintaining the correct balance of the various cellular genotypes and phenotypes in culture can be quite challenging and can be a factor that contributes to irreproducible results. Studies at different laboratories that use the same cell lines often show different experimental results, even when using the same methodology. The reliability of experimental outcomes and the inconsistencies among laboratories are impacted by many factors, including changes in morphology, population doubling levels (PDLs), passage number, microbial contamination and cross-contamination/identification of cells.

The adaptation of best cell culture practices in the management of cell lines can preserve the various phenotypes and genotypes within the culture population, thereby making the cell lines more useful for basic and translational research applications while ensuring reliable and reproducible results across laboratories. Through periodic testing and proper cell culture management, misidentified and contaminated cell lines can be identified before publication of results or release into the scientific community, thus protecting the validity of research results and the credibility of the biomedical community as a whole.

Best Practices

Growth Medium

Different cell lines can require specialized growth medium that is unique to the tissue of origin, one that maintains expression of the desired genotypes and phenotypes. For example, a cell line established from a breast tumor will require a different growth medium from one established from a prostate tumor because they have different growth requirements. Furthermore, a change in growth medium will induce changes in how the cells behave. In terms of lot-to-lot variation, a fully chemically defined media formulation is the “gold standard” for reproducibility. However, most cell lines used in research labs and even some lines used in clinical applications are cultured using undefined fetal bovine serum and/or native or recombinant growth factors, all of which can be highly lot-specific.

When using these basal media supplements they should be qualified to ensure that any lot variation is not causing changes within the cells.

Morphology

It is strongly recommended that cell morphology and behavior be observed and recorded frequently in order to track changes and monitor the health of cells in culture. Observation by microscopy is the simplest and most direct method. The value of this method is greatly enhanced by the addition of photographic or electronic imaging, data storage, and analysis. Observations of the cultures should be made at the same cell density and growth stage, using the same medium and substrate. A change in morphology can signal deterioration of the culture and often indicates that the cells are differentiating, are contaminated by microorganisms or with another cell line, or are undergoing crisis or senescence. For example, the murine 3T3 fibroblast and C2C12 myoblast cell lines differentiate into adipocytes and myotubes, respectively, when they are confluent.

Optimum Growth Condition

The establishment of a growth curve can offer valuable information about a cell line, including optimal growth conditions such as temperature, pH, and substrate. A change in morphology can signal deterioration of the culture and often indicates that the cells are differentiating, are contaminated by microorganisms or with another cell line, or are undergoing crisis or senescence. For example, the murine 3T3 fibroblast and C2C12 myoblast cell lines differentiate into adipocytes and myotubes, respectively, when they are confluent.

Passaging

Passaging should be considered an aging process; therefore, the higher the passage number, the older the cells. The effects of long-term culturing, or increased passaging, on a cell line can include changes in morphology, development and gene expression. Furthermore, selective pressures may lead to genotypic and phenotypic instabilities, which could result in genomic and mitochondrial DNA analysis is also an effective method, the human Caco-2 cell line has demonstrated passage-related variations in growth rates and transcellular electrical resistance. Furthermore, cell contamination is often missed when the human telomerase reverse transcriptase may develop small clonal populations of aneuploid cells at high passage number. If this environment is not controlled, it is possible that these small clones could expand and take over the culture.

The creation of a master cell bank or a seed stock is strongly recommended to help maintain reproducibility of results. The master cell bank/seed stock should be established upon receipt of a new cell line with initial verification of the species, correct genotype and phenotype and stock free of microbial contamination. This bank will enable a researcher to work with cells in an optimal PDL or passage range for an extended period of time as they can effectively “go back in time” and use cultures that are at the same PDL or passage over an entire project.

Misidentified or Contaminated Cell Lines

Cross-contamination or misidentification of cell cultures is a problem that has plagued the biomedical field for decades. In most cases, cell lines are assumed to be correct based on the reputation of the source, and are therefore not routinely tested for interspecies or intercellular contamination. When performing research with any cell line, it is best practice to ensure that the cell line is not contaminated and is correctly identified. For example, cytotoxicity and oxidative stress analysis can be used to verify the species of origin and reveal contamination by another line of different species while short tandem repeat analysis can serve as an effective method to ensure the validity of cell lines.

Microbial contamination is frequently evident to the naked eye; however, a low-level of contamination is often missed. The most common microorganisms can typically be detected through microbial testing. For example, bacterial and fungal tests will detect the most fastidious organisms known to infect cell cultures and media.

Mycoplasma contamination can have a harmful impact on cell function, and can invalidate research findings. The NIH now requires grant applicants to describe how they will authenticate their cell lines, and journals such as Nature and others now require authors to authenticate their cell lines as a prerequisite for publication. Furthermore, journals now encourage more detailed information in the supplemental sections, including culture methods, cell authentication and mycoplasma testing. Without these efforts, it is almost impossible to reproduce results across laboratories—and to prevent erroneous results from being published in literature.

Summary

Many tumors are quite heterogeneous and the cell lines derived from these tumors generally reflect this heterogeneity. Preserving this heterogeneity in cell culture is critical as it best reflects the tissue of origin; however, this can be a factor that leads to irreproducible results. There are various culture conditions that impact cell heterogeneity, including increased passages, suboptimal growth conditions, cellular cross-contamination or microbial contamination, and each of these factors can be addressed through the adoption of best practices in cell culture research. Research projects are at risk of producing inconsistent or irreproducible results if researchers fail to incorporate these necessary best practices in their research activities.

Mindy Goldsborough, Ph.D., is ATCC’s chief science and technology officer and vice president of ATCC Cell Systems, ATCC’s R&D business focused on optimizing and innovating cell- and cell biology-based products. Dr. Goldsborough, who has a Ph.D. in molecular biology, has served as ATCC’s manager and scientist, was a key contributor to this article.

The opinions expressed in guest commentaries do not necessarily represent those of DDNews and/or its owners, editors or other staff.

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**RESEARCH & DEVELOPMENT**

**BRIEFS**

**A boost for biomanufacturing**

**CAMBRIDGE, U.K.**—In its efforts to support biologic therapeutic manufacturing at home and abroad, Hookipa Discovery Group plc has inked new partnerships with the Centre for Process Innovation (CPI) and the National Institute for Bioprocessing Research and Training (NIBRT). Under the license agreement, any organization can access Horizon’s biomanufacturing cell lines, through CPI or NIBRT, for research purposes. Horizon is developing cell lines for manufacturing a variety of current and next-generation biological therapeutics and hopes to boost innovation in other companies by offering access to its bioproduction cell line platform, called CHO SOURCE.

“Horizon is committed to driving innovation in bioprocessing,” Darrin Disley, CEO of Horizon Discovery, said in a press release. “We value the opportunity to work with key industry players, including CPI and NIBRT, to ensure that we are delivering the best solutions for our customers and ultimately for patients.”

**FVG awards €4.16M grant to Hookipa**

**VIENNA, Austria**—Hookipa Biotech AG has received its fifth major grant from the Austrian Research Promotion Agency (Forschungs-Förderungs-Gesellschaft, or FFG), the top public funding agency for translational research in Austria. The grant, awarded for the second year of a multyear research and development project, is worth €4.16 million. Hookipa will apply the funds to continue demonstrating the broad applicability of its arenaviral vector technologies in developing cancer immunotherapies and for further development of HB201, its lead oncology candidate for the treatment of HPV-associated head-and-neck cancer.

Joern Aldag, CEO of Hookipa, commented, “After having successfully started a clinical Phase 1 study for our cytomegalovirus vaccine candidate earlier this year, we are now actively working towards expanding the use of our technologies into the field of immuno-oncology. FFG’s steady support of this project will help us to accelerate development of urgently needed cancer therapies.”

**New research into NR**

ChromaDex says nicotinamide riboside is essential to cellular energy production

**BY RACHEL FLEHINGER**

**IRVINE, Calif.**—New discoveries in the quest for a more healthful aging process have emerged from ChromaDex Corp., and along with this, the company has released findings indicating that nicotinamide riboside (NR) is an essential precursor to cellular conversion to NAD+ (NAD being nicotinamide adenine dinucleotide and NAD+ the oxidized version). ChromaDex markets and sells nicotinamide riboside as an ingredient under the brand name Niagen.

“The body of scientific evidence confirming the importance of NAD+ in promoting healthy aging is overwhelming. With this established, we have seen the conversation shift from ‘How important is NAD+’ to ‘How do we most efficiently and effectively boost NAD+?’ NR continues to prove itself the leader over and over again,” says ChromaDex Founder and CEO Frank Jaksch. NAD+ is a cellular co-enzyme critical for cellular metabolism.

**Two-pronged response**

**MIT advancement in immunotherapy fights cancer in mice**

**BY ILENE SCHNEIDER**

**CAMBRIDGE, Mass.**—Between August 1, 2015, and July 31, 2016, the U.S. Food and Drug Administration approved 13 new anticancer therapeutics, including four new immunotherapeutics and four new molecularly targeted agents, according to the AACR Cancer Progress Report 2016. Activation immunotherapies induce or amplify an immune response and are used in vaccines and as cancer immunotherapies, explains Nature Medicine.

An article in the latter (“Eradication of large established tumors in mice by combination immunotherapy that engages innate and adaptive immune responses”) by Kelly D. Moynihan, Cary F. Opel and colleagues, published online in late October, demonstrates how a new advancement from the Massachusetts Institute of Technology (MIT) could bring cancer immunotherapy closer to the core in oncology therapeutics. Researchers used a combination of four different therapies to activate both of the immune system’s two branches, producing a coordinated attack that led to the complete disappearance of large, aggressive tumors in mice, according to MIT. Potentially allowing patients to receive treatment for a cancer diagnosis earlier in the disease process, these findings may lead to safer and more effective cancer treatments in the future. Researchers hope that their discoveries may provide a way to activate different immune cells to operate in concert, allowing them to fight off tumors in an effective, coordinated manner.

**CC TIPS**

**Lipid profiling steps up a notch**

Multi-lipid profiling highlighted as potential new pathway for COPD biomarker development

**BY DDNEWS STAFF**

**NEUCHÂTEL, Switzerland**—This fall, a study published in the International Journal of Molecular Sciences, titled “Alterations in serum polyunsaturated fatty acids and eicosanoids in patients with mild to moderate Chronic Obstructive Pulmonary Disease (COPD),” demonstrated the potential of multi-lipid profiling to support future biomarker development for COPD. Combining lipidomic profiling with computational network biology analyses, researchers were able to build a comprehensive and quantitative picture of the lipidome that is capable of distinguishing cigarette smokers from non-smokers, with improved separation of smokers that were symptomatic of mild to moderate COPD. This study has clearly demonstrated that there are many lipids, beyond those conventionally measured in the clinic, that are responsive in the section of society most at risk of COPD, i.e., cigarette smokers,” said Dr Björn Titz of the Computational Biology division of Philip Morris International (PMI), a tobacco company that has been delving in the life-sciences realm in recent years, particularly through the IMPROVER program. “Lipidomic information relating to smoke exposure and COPD has until now been relatively sparse. At the same time, markers discovered by lipidomics for other conditions are starting to make their way into the clinic. As such, this study should be highly relevant to scientists working in COPD from the point of view of biomarker development or personalized medicine.”

The study was designed to identify a biomarker, or panel of biomarkers, suitable for the differentiation of four groups: COPD CONTINUED ON PAGE 14
**CELLULAR**

Continued from Page 12

energy production and mitochondrial health. NAD+ activates cellular metabolism and energy production within the cell’s “power stations,” the mitochondria. Mitochondria are constantly working to convert the food we eat into the energy necessary to power all bodily systems as well as help us stay healthy enough to ward off illness. The challenge is that both NAD+ levels and mitochondrial functions decline as we age, fueling research into strategies for NAD+ repletion with B3 vitamins in order to maintain a youthful metabolism. Recent work that appeared in *Nature Communications* demonstrated that NR is not only the most efficient and effective B3 at upregulating NAD+, but it is also the most effective activator of longevity-promoting sirtuin proteins.

In 2011, Cornell University granted ChromaDex exclusive worldwide rights to a novel manufacturing process for NR, a vitamin found in milk that is a more potent version of niacin (or vitamin B3). Like niacin, NR is a precursor to NAD. Increasing cellular NAD has been shown to have cell-protective and physiological decline in mammals. Brenner noted, “Anything NNM does, NR is going to be able to do because NNM must become NR to get into cells.”

“Neither NNM, niacin nor nicotinamide are more efficient than NR at boosting NAD+. Mega-doses of nicotinamide and ribose are not equivalent to NR because high doses of nicotinamide inhibit sirtuin activities.”

Dr. Charles Brenner, a NAD+ researcher to NAD+, without the presence of NRK1. These results explain why NR and NNM have similar benefits in protecting against metabolic disease, neurodegenerative disorders and physiological decline in mammals. Brenner stated, “Anything NNM does, NR is going to be able to do because NNM must become NR to get into cells.”

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Roughly 10 years’ worth of preclinical research, together with recent clinical work in humans, have shown that supplementing with NR effectively boosts NAD+ levels. Brenner noted in a press release that “Neither NNM, niacin nor nicotinamide are more efficient than NR at boosting NAD+,” and that “Mega-doses of nicotinamide and ribose are not equivalent to NR because high doses of nicotinamide inhibit sirtuin activities.”

**EDITCONNECT: E121608**
Synaffix inks commercial deal with ADC

AMSTERDAM, the Netherlands—Late October saw Synaffix BV announce an amendment to its Commercial License Agreement with ADC Therapeutics for its proprietary GlycoConnect and HydraSpace site-specific antibody-drug conjugate technologies.

Under the terms of the agreement, ADC Therapeutics has been granted a worldwide non-exclusive license to three of its preclinical programs and has also been granted an option to take a limited number of additional single-target licenses for potential future programs.

“We are delighted that ADC Therapeutics has recognized the value of our GlycoConnect and HydraSpace conjugate technologies and has elected to incorporate Synaffix technology into one of its preclinical programs,” said Floris van Delft, chief scientific officer at Synaffix. “The experience of Synaffix and its partners has consistently confirmed that, in clinical trials, our proprietary GlycoConnect and HydraSpace technologies significantly improved both efficacy and safety as compared to other mainstream site-specific conjugation approaches.”

The ProCTOR model worked best when data about the drug’s target was included; however, the authors note that this information is not always available during drug development. Moreover, many drug companies don’t release details about why a particular drug failed a clinical trial.

For us, the more data the better,” says first author Katelyn Geyser, a Ph.D. student in the Tri-Institutional Computational Biology and Medicine Program, a partnership of Weill Cornell Medicine, Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center. “If better clinical trial data is reported in the future, we’ll be able to make better predictions.”

“Absence of clinical trial reporting means we are not able to learn from trial outcomes. Likewise, mechanisms of drug action in cells are not always well defined. To address this problem, we are working on artificial intelligence-guided methods to predict drug targets with high accuracy, including off-targets,” Elements adds.

Because ProCTOR is a machine-learning-based tool, it provides an opportunity to predict more than just a toxicity score. According to Elements, “We are working to predict specific types of toxicity, such as liver or cardiac toxicity. Our initial results look promising.” The models are fully validated, they would pave the way for 1) guiding clinical trials by enrolling only patients at low risk of certain toxic events and 2) enhancing post-approval drug surveillance by focusing on specific types of adverse events and toxicity in patients receiving a particular molecule.”

“We believe that artificial intelligence-guided methods such as ProCTOR will increasingly provide new insights into how to optimally design drugs that are safe and highly effective. We envision that ProCTOR will be applied early in the drug development process to help guide optimization of properties that dictate toxicity. ProCTOR can also be used for increased post-approval drug surveillance for drugs flagged with a high likelihood of toxicity,” Elements says.

“As discussed, we are working on a battery of other methods to help speed up the process of discovering and developing new drugs, learning how to combine these, and identifying the markers of response and starting to partner with pharma companies to test and apply these methods.”

COPD CONTINUED FROM PAGE 12

smokers with mild to moderate COPD, healthy smokers, individu- als with COPD who have never smoked, and individuals who have quit smoking for a year or more.

Leveraging a network biology analysis approach, the authors identified the main lipidomic trends between smokers and non-smokers: a general increase in glycyrrhizin, a compound from the drug’s main component of all biological membranes, e.g., cell membranes), changes in fatty acid saturation (a decrease in polyunsaturated fatty acids, an increase in mono-unsaturated fatty acids) and an imbalance in eicosanoids (signaling molecules that help control over many bodily systems). These effects often appeared amplified and more significant in smokers who had COPD in comparison to the group of smokers without COPD. However, the COPD group was also associated with a higher cumulative smoking exposure than the healthy smoking group, so it remains unclear which effects are more closely linked to COPD, rather than being the result of more extensive cigarette smoke exposure. This suggests that the future study of former smokers with COPD may help to identify effects that are more specifically related to COPD itself, rather than cigarette smoking. This study has yielded important new insights into the complex interplay between cigarette smoke exposure, lung disease and alterations in lipid profiles,” said Dr Julia Hoeng, director of systems toxicology and research in the Biological Systems Research Unit at PMI. “In addition, it identifies new avenues for research in the ongoing quest to identify a robust biomarker for COPD and to better identify all smokers whose discovery would entail, from diagnostics, to drug discovery, to personalized medicine.”

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“Lipidomic information relating to smoke exposure and COPD has until now been relatively sparse. At the same time, markers discovered by lipidomics for other conditions are starting to make their way into the clinic.”

Dr Björn Titz of PMI smoking group
ADI-PEG 20 can boost antitumor immune surveillance

SAN DIEGO—Polaris Group announced recently that ADI-PEG 20, arginine deiminase formulated with polyethylene glycol, can boost antitumor immune surveillance. The company’s research findings suggest that ADI-PEG 20 could potentially enhance the activity of antitumor immune therapies, including checkpoint inhibitors.

To investigate the potential effect of ADI-PEG 20 on immune cells, healthy human peripheral blood mononuclear cells were treated with ADI-PEG 20 under resting and activation conditions and were characterized by immune cell phenotyping using flow cytometry. Researchers found that under stimulation conditions ADI-PEG 20 treatment markedly boosted T cell activation (as measured by CD69 expression) while moderating T cell exhaustion (CTLA-4 and PD-1 levels remained low, similar to that at a resting state). Moreover, ADI-PEG 20 reduced accumulation of regulatory T cells, which are immunosuppressive and generally suppress or downregulate induction and proliferation of effector T cells. As such, it was hypothesized that ADI-PEG 20 may improve immunogenicity of non-immunogenic tumors.

The poorly immunogenic mouse melanoma B16-F10 model was used to test the hypothesis. Analysis of the tumor sections revealed that five out of six ADI-PEG 20 treated animals had a large number of T cells in their tumors; only one ADI-PEG 20 treated mouse had very little tumor T cell infiltrate, similar to the non-treated controls, demonstrating that ADI-PEG 20 can improve tumor immunogenicity. ADI-PEG 20 also inhibited growth of the B16-F10 tumor in vitro and in vivo.

“We are excited about the discovery of ADI-PEG 20’s ability to regulate cellular immune response, thereby expanding its mechanism of action for its antitumor activity. We are conducting further research to assess which combinations of ADI-PEG 20 with PD-1/ PD-L1 blockers will further enhance these drug’s antitumor efficacy,” said Dr. John Bomalaski, executive vice president of medical affairs at Polaris Pharmaceuticals Inc.

MIT

CONTINUED FROM PAGE 12

The targeting of many types of cancer, the approach may enable the immune system to “remember” the target and destroy new cancer cells that appear after the original treatment.

Because tumor cells usually secrete chemicals that suppress the immune system, it can be difficult for the body to attack tumors on its own. In order to overcome that, scientists have attempted to discover ways to provoke the immune system into action. Most of the efforts have been focused on the innate immune system and the adaptive immune system. The innate system includes nonspecific defenses such as antimicrobial peptides, inflammation-inducing molecules and cells such as macrophages and natural killer cells.

Researchers have attempted to enable this system to attack tumors by delivering antibodies that latch onto tumor cells and recruit the other cells and chemicals needed for a successful attack.

“We have shown that with the right combination of signals, the endogenous immune system can routinely overcome large immunosuppressive tumors, which was an unanswered question,” explained Darrell Irvine, a professor of biological engineering and of materials science and engineering and a member of MIT’s Koch Institute for Integrative Cancer Research. Irvine and Dane Wittrup, the Carbon P. Dubbs Professor of Chemical Engineering and Bioengineering and a member of the Koch Institute, are the senior authors of the study.

While therapy with antibodies specific for certain kinds of tumors causes “durable tumor regression in metastatic cancer,” these “dramatic responses (programmed cell death) are confined to a minority of patients,” the article said. “This suboptimal outcome is probably due in part to the complex network of immunosuppressive pathways present in advanced tumors, which are unlikely to be overcome by intervention at a single signaling checkpoint.”

Instead, the researchers used a “combination immunotherapy that recruits a variety of innate and adaptive immune cells to eliminate large tumor burdens in syngeneic tumor models and a genetically engineered mouse model of melanoma.” The methodology used four components: a tumor-antigen-targeting antibody, a recombinant interleukin-2 with an extended half-life, anti-PD-1 and a powerful T cell vaccine. The treatment “induced infiltration of immune cells and production of inflammatory cytokines in the tumor, enhanced antibody-mediated tumor antigen uptake and promoted antigen spreading.”

The MIT researchers tested the combination treatment in mice implanted with three different types of tumors: melanoma, lymphoma and breast cancer. Such engineered tumors are harder to treat than human tumors implanted in mice because they suppress the immune response against them. Researchers found that in all of these strains of mice, about 75 percent of the tumors were completely eliminated. When the researchers injected tumor cells into the same mice six months later, they found that their immune systems were able to completely clear the tumor cells.

The research was funded by the Koch Institute support core grant from the National Cancer Institute, the National Institutes of Health, the Bridge Project partnership between the Koch Institute and the Dana-Farber/ Harvard Cancer Center, the V Foundation and the Ragon Institute of MGH, MIT and Harvard.

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Onxo announces promising potential for Beleodaq

Combining agent with checkpoint inhibitors expands therapeutic possibilities for tumor treatment

BY RACHEL FLEHINGER

PARIS—Biopharmaceutical company Onxo, best known for pharmaceuticals designed to treat orphan diseases, particularly in oncology, has uncovered what it says is dramatic potential for its drug Beleodaq in combination with checkpoint inhibitors in treatment against tumor growth. The study found that when combined with checkpoint inhibitors in mice, Beleodaq caused a 100-percent cessation of tumor growth.

Beleodaq, the trade name for belinostat, was FDA-approved in 2014 as a second-line treatment for patients with peripheral T-cell lymphoma, a rare and fast-growing type of non-Hodgkin’s lymphoma, based on its tumor response rate and duration of response. The drug works by inhibiting histone deacetylases, preventing the T cells from becoming cancerous.

In conjunction with the University of Navarra’s University Clinic and the Center for Applied Medical Research in Spain, Onxo has been exploring the combination of various compounds, including PD-1 and CTLA-4 checkpoint inhibitors, with Beleodaq in order to assess the synergistic effects on the activation of the immune response in several types of solid tumors.

Preclinical studies were performed in a pre-existing mouse syngeneic hepatocellular carcinoma model, in which responses to a combination of Beleodaq and checkpoint inhibitors were compared to responses from treatment with checkpoint inhibitors alone.

“What makes these findings particularly exciting is the fact that all mice responded to the combination therapy,” says Dr. Graham Dixon, chief scientific officer of Onxo. “Our team is impressed by the 100-percent cessation of tumor growth during treatment, especially because Onxo continued on page 18

Healing ahead with Hsp60?

A topical treatment of the protein heals wounds in diabetic mice in just three weeks

BY KELSEY KAUSTINEN

BETHESDA, Md.—A newly elucidated function of a well-known gene, heat shock protein 60 (Hsp60), might offer a new approach to wound healing. Researchers from the National Institutes of Health—specifically the National Human Genome Research Institute (NHGRI), the National Eye Institute (NEI) and their colleagues—found that Hsp60 plays a key role in the body’s inflammatory response in the face of injury. The results of their work appeared in the paper “Extracellular Hsp60 triggers tissue regeneration and wound healing by regulating inflammation and cell proliferation,” which was published in Regenerative Medicine.

The proteins produced by the Hsp60 gene are generally known for ensuring that other proteins fold properly, and the Hsp60 protein is known to function as a signaling molecule to induce an inflammatory response to bacterial infection in wounds.

Dr. Shawn Burgess, head of NHGRI’s Developmental Genomics Section and senior author on the study, tells DDNews this was the first time his lab had worked with Hsp60, and that this work has its roots in a study published four years ago. His lab focuses primarily on studying zebrasiphon (known for their ability to regenerate a variety of tissues) and hearing regeneration. In Hsp60 continued on page 17

Cutting the fat to treat cancer

Salk Institute researchers and collaborators develop novel cancer treatment that halts fat synthesis in cells, stunting tumor growth

BY MEL J. YEATES

LA JOLLA, Calif.—Fat isn’t just something we eat; it may also lie at the heart of a new approach to treating cancer.

Cells create their own fat molecules to build their plasma membranes and other critical structures. Now, researchers at the Salk Institute, along with academic and industry collaborators, have found a way to obstruct this instrumental process to stifle cancer’s growth, which they detailed in a paper published Sept.19 in SALK continued on page 18

IN THIS SECTION

BRIEFS

CPI-444 shows promise two ways

BURLINGAME, Calif.—Biopharmaceutical company Corvus Pharmaceuticals Inc. debuted encouraging preclinical data and preliminary biomarker data from its ongoing Phase 1/1b study of CPI-444 at this year’s CPI-MNT-EAST-AACR International Cancer Immunotherapy Conference: Translating Science into Survival. The study is evaluating CPI-444, a potent and selective inhibitor of the adenosine A2A receptor, as a single agent and in combination with Genentech’s TECENTRIQ (atezolizumab), a fully humanized monoclonal antibody targeting PD-L1. As reported at the conference, CPI-444 has been found to be active as both a single agent and in combination with anti-PD-1 and anti-PD-L1 antibodies at stimulating immune cells, generating anti-tumor immunity, suppressing tumor growth, delaying tumor progression and generating total tumor rejection in animal models of cancer. CD8+ cytotoxic T lymphocytes have been found to be necessary for the compound’s activity, and animals previously treated with CPI-444 showed long-term immunity upon tumor re-challenge.

Expanded mouse models from JAX

BAR HARBOR, Maine—The Jackson Laboratory (JAX) has expanded its offerings with the launch of its Model Generation Services, a comprehensive suite of genome-editing technologies that can enable custom-made mouse models for the study of disease. JAX has also added CRISPR/Cas9-mediated gene editing into its development of custom-built mouse models. Model Generation Services include CRISPR/Cas9 Model Generation, to enable customers to develop knock-out and knock-in models; Transgenic Model Generation, to enable customers to overexpress novel gene constructs in defined inbred strain backgrounds via pronuclear microinjection; and ES Cell Microinjection Services, for the creation of large, targeted genomic mutations in various genetic backgrounds.

“CRISPR technology has transformed genetic engineering in nearly all biological systems,” said JAX President and CEO Dr. Edward Liu. “Applying this technique to build more predictive preclinical models and precise patient treatment strategies will be pivotal in developing the next generation of predictive models for the new era of personalized medicine.”

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Wound healing

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HSP60

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The aforementioned study, the team used transcriptional profiling to find all the genes that turn on or off in zebrafish during healing regeneration, he explains, and identified 2,000 genes. They then started using CRISPR/Cas9 to systematically knock out all of those 2,000 genes. Burgess reports that they have gone through 250 genes so far, and found eight genes that affect regeneration, one of which was Hsp60.

“Because HSP60 has a well-known role as a protein chaperone, we were a little surprised how strongly the block in regeneration was when we KO’d Hsp60,” Burgess admits. “There was no regeneration at all, and that extended to other tissues such as the tail fins, which also did not regenerate in the mutants. We found an old paper from Mark Keating’s lab that showed a similar effect in zebrafish tail regeneration in an Hsp60 mutant they identified in a screen for regeneration mutants … We did some research in the literature and found out that extracellular Hsp60 was shown to cause inflammation. We checked the inflammation response in our Hsp60 mutant fish and saw that it was lower than normal. Inflammation has been shown to be essential for wound healing, so we wondered if Hsp60 was sending a specific signal to the innate immune system to stimulate wound healing.”

The team knocked out Hsp60 in zebrafish and found that while the mutant fish developed normally, when they faced a wound—either an injury to the cells involved in healing or the amputation of a caudal fin—they could not regenerate the damage. Burgess and his team then used fluorescently tagged leukocytes to show that when Hsp60 was knocked out, there were noticeably fewer of these immune cells at the injury site. However, when Hsp60 was reintroduced to the area, either injected directly to the injury site or as a topical treatment, regeneration started up again. When the topical treatment was applied to a puncture wound in animal models, the diabetic mice saw complete healing after just 21 days.

Wound healing is a chronic problem for diabetic individuals, as roughly 15 percent of diabetics develop a foot ulcer at some point. These ulcers result from a variety of factors, including reduced sensation, poor circulation and skin irritation. High blood glucose levels can result in diabetic neuropathy, in which damaged nerves lead to a loss of sensation, and atherosclerosis, which can hamper circulation to extremities. Foot ulcers can become serious and in some cases lead to amputation; in fact, diabetes is the top cause of non-traumatic lower limb amputation in the country.

As for why diabetics suffer from impaired wound healing, Burgess explains that “There is some recent evidence that the diabetic wound response is a hyperactive inflammation response. In particular, there seems to be a near-catastrophic overstimulation of neutrophils at the wound site, but macrophages are also involved. A key concept in inflammation is ‘inflammation resolution,’ i.e., the immune response needs to know when to stop attacking the wound site (primarily an anti-infection response) and let it heal.”

“It does seem counterintuitive that a protein that increases inflammation could help injuries that are a result of overactive inflammation but again, resolution of the inflammatory response is the important idea,” he adds. “Generally speaking, there are two ‘phases’ for macrophages: M1 macrophages, which are an attack mode for injury sterilization, and M2 macrophages, which stimulate wound healing and tissue regeneration. It turns out that Hsp60 appears to bring in M2 macrophages (or convert M1 to M2). So we think in the case of diabetes, the Hsp60 is allowing the inflammation response, which has been locked into M1 phase, to resolve into M2 and continue normally along the wound-healing process.”

Burgess says the team plans to explore multiple avenues as they move forward, including if the results seen with topical Hsp60 treatment will translate to humans and help heal any wound. They hope to identify “the exact receptor (or receptors) that HSP60 is being bound by that triggers this wound healing response,” and hope to find researchers interested in moving this work into the clinic to see if it could help individuals with diabetic ulcers. They also aim to identify the downstream responses Hsp60 triggers in macrophages, he notes, and intend to continue their work in knocking out the rest of the 2,000 genes in hopes of identifying others that play a role in triggering regeneration.

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The research has produced another key finding of interest to oncology treatment. Studies performed on the spleens of the mice demonstrated the generation of an underlying immune response that correlated with the observed therapeutic effect of the combination treatment, showing an increase in interleukines (chemical messengers that control cell migration and activation) by activated T cells and a decrease in CD8+ T cells, when compared to mice treated only with checkpoint inhibitors.

“Our ability to measure the increase and decrease in T cells resulted in a deeper understanding at a mechanistic level of the inflammatory response, adding evidence to what we already know about the benefits of the combination therapy,” says Onxeo CEO Judith Greciet.

In the next step of the collaboration with University of Navarro experts Prof. Bruno Sangro and Dr. Pablo Sarobe, Onxeo will conduct follow-up studies to explore the product’s potential with other cancer agents in specific cytotoxic cancers. “We [seek to] fully characterize these preclinical findings demonstrating the potential of Beloqad in combination with checkpoint inhibitors in various tumor indications, and in particular, we are evaluating the immune response in the tumor microenvironment in order to improve the translation of the response into human patients,” says Dixon.

Onxeo specializes in the development of innovative drugs for the treatment of orphan diseases, driven by high therapeutic demand in one of the fastest growing segments of the pharmaceutical industry. Beloqad joins its orphan oncology pipeline, which also includes Livatag, in Phase 3 trials for the treatment of hepatocellular carcinoma; AsidNA, which has successfully undergone a proof-of-concept Phase 1 trial to treat metastatic melanoma; and Validive, currently in Phase 2a trials to treat head-and-neck cancer patients with severe oral mucositis.

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Lessons from first-generation biologics inform the evolution of the next

BY RANDALL C WILLIS

If there is one technology that is evolving faster than its end-users’ needs, it has to be the telephone. A device that once literally tethered its user to a wall evolved into a portable if bulky electronic shoebox. And as circuitry evolved, so too did the size of the phone, to the point where it can now be secretly palmed from user to user. And perhaps more aggressively than its physical form, the applications of telephonic technology have changed rapidly. What was once simply a device for transmission of verbal communication became a mechanism to maintain a personal calendar, exchange emails and text messages, and eventually, to take unplanned photographs at the ends of retractable sticks.

Today, there are so many apps available to phone users that the handheld device—when not secreted over an ear—has become everything from a gaming console to a digital publishing platform to a living record of mundane daily existence. And every now and again, it is even a telephone.

If there is a biotechnology equivalent to the telephone, it is likely the antibody, which outside of its natural biological functions within each of us, served for many years as a detection platform for proteins on gels and pathogens in environmental and medical samples.

It too evolved, however, in the medical sphere to become a vital component of the therapeutic armamentarium, being injected and infused into patients to modulate the activity of cell surface markers linked to everything from cancer to autoimmune disease.

As the first generation of antibody therapeutics go off patent, new applications arise to expand the repertoire of functions for the basic antigen-binding platform, whether in the form of smart-bomb antibody-drug conjugates (ADCs) or immune-cell-recruiting multispecific complexes or reductionist fragment-based therapies.

Cloak and dagger

“The concept of ADCs has been around since before the advent of monoclonal antibodies,” says Peter Senter, vice president of chemistry at Seattle Genetics. “But putting it into practice was very difficult because a lot of the clinical parameters for making things work weren’t really well understood.”

“Several molecules had gone into clinical testing that looked like they might be interesting based on preclinical studies, but they turned out to be fairly toxic and ineffective,” he continues. “So, we picked it apart and looked at the impact that drug potency had, the impact that linker stability had, conjugation chemistry, pharmacokinetics and antibody specificity.”

The result for Seattle Genetics was FDA approval of one of the two ADCs currently on the market: CD30-directed Adcetris (brentuximab vedotin) for Hodgkin’s lymphoma and systemic anaplastic large cell lymphoma.

As Senter suggests, the original idea of ADCs was to use the antibody to simply deliver a toxic payload to the cells carrying specific targets. Upon entry to the cell, the payload would be released and the cell would be destroyed. In part, this is why ADC research has focused so heavily on cancer where cell surface receptors are often over-expressed relative to nearby healthy cells (see also sidebar “Not just cancer” on page 22).

But while this is one mechanism of activity of ADCs, Senter continues, the story may be much more complicated than originally thought.

“What we’ve discovered using ANTIBODY-CONTINUED-ON-PAGE-20
heterogeneous tumor models is that once the drug is released inside the target cell, it cannot only stay there, but diffuse out and affect cells in the neighboring vicinity that might be antigen-negative," he adds. In this case, treatment triggers changes in the target cell and the release of soluble signals that attract T cells to the tumor, prompting an immune response.

"In a general sense, the field is looking very promising, because there are more than 50 ADCs in various stages of clinical development," Senter enthuses. "And many of them are showing very pronounced activities."

"There's our drug" he lists. "There's Kadrylca from Genentech, Roche, an approved drug. And then there are other agents in Phase 3 clinical testing on a variety of different types of malignancies that look rather encouraging."

Even with only two products on the market, a report published in July suggested that the ADC market in 2015 was worth about $900 million. Furthermore, by 2025, this value could rise to $10 billion with the expected commercial launch of another 10 ADCs. And the prospect of another 60 or so therapeutic candidates in preclinical and discovery-stage development bodes well for the market.

But, as with any biotechnology effort, there is a great distance between discovery and market, and this may be particularly true for ADCs, which are particularly complex molecules.

Into the weeds

ADCs have a lot of working parts—targeting mechanism, payload, linker—and as Senter suggests, optimizing each of those components is essential to generate a viable therapeutic.

The choice of the drug component can be critical to the success of an application of an ADC, particularly in cases of multidrug resistance (MDR), explains Gregory Adams, chief development officer at Eleven Biotherapeutics.

"If you have treated a patient who has breast cancer for a long time with a chemotherapeutic regimen, you could have a situation where the MDR, with its P-gp regulatory function in tumor cells," he says. "Then you come in with ADC and that drug payload, once it gets off the anti-body in the lysosome and mixes into the cytosol, is pumped out of the cytosol by the MDR pump."

With this in mind, Eleven’s lead candidates are fusion proteins that include a targeting portion—a Fab or single-chain antibody—linked to a peptide payload as a single gene product that can be expressed in E. coli.

"Our payloads, while they’re not huge, are too large to be pumped out of the cells via these pumps," Adams explains. "So, once we get into the cytosol, we stay there."

"It means that we’re not going to detonate the payload within the tumor cells, but it also means you’re not going to have a bystander effect on nearby cells that you don’t want to hit," he adds. "For instance, if you’re going after head-and-neck cancer, you worry about the nerves."

Oncomyxa, meanwhile, has addressed MDR-related issues by focusing on synthetic cytotoxins, small tetrapeptide payloads that are highly cytotoxic and anti-angiogenic, while also being flexible for a variety of linker technologies and can be synthesized in sufficient quantities for clinical development. Just as importantly, however, is the fact that these compounds—derivatives of natural cytotoxic tubulins, which inhibit tubulin polymerization—are not substrates for MDR proteins.

The company has conjugated the payload to anti-MTX5 antibodies, testing the ADCs against xenograft murine models of pancreatic cancer and noted 100-percent tumor growth inhibition when used as a monotherapy and tumor regression when used in combination with gemcitabine and/or abraxane. MTX5 is a membrane glycoprotein found predominantly in cancer-associated fibroblasts.

One of the challenges of tubulin-disrupting compounds, however, is the abundance of tubulin naturally occurring within cells. Thus, disruption requires high concentration of drug to be internalized and released.

To overcome such challenges, many companies are exploring the use of DNA damaging and interfering compounds such as pyrrolobenzodiazepines (PBDDs) or, in the case of NBE Therapeutics, an arylmaleimide-based drug related to doxorubicine, which it labels PNU-156982. Using its conjugation platform SMAC-Technology, the company enzymatically links PNU to the C-termini of the antibody’s light and heavy chains via sortase and poly-glycine-modified payload.

The company has a variety of candidates for both solid and soft tissue tumors that are heading into preclinical development, and in October, it announced an agreement with the latter company pick up clinical development of any new ADCs arising from the collaboration.

Ironically, in something of a twist on the typical pharmaceutical thinking, therapeutic efficacy is often very dependent on payload toxicity.

“When you do systemic delivery with an ADC or antibody, you don’t get the majority of the antibody and the payload to the tumor; the majority of it goes elsewhere and is processed by the normal tissues,” Adams says. “You get a small fraction into the tumor, so you have to make it as potent as possible and as safe as possible. I think something like 0.1 to 0.01 percent injected dose per gram of tissue, which is really not that much.”

The key is to find that window set for that payload to be as toxic as possible because you’re going to get a little more focus on delivery to tumors, he presses. "In fact, our xenografts and our preclinical payloads are often payloads that failed as single agents without the antibody because they were too toxic.”

Another important factor is how many of the drug molecules will be loaded onto the antibody: the drug-antibody ratio (DAR),” Nikolaos Diamanti, head of a humanized antibody at London’s Institute of Cancer Research explained. "Thus, the currently licensed ADCs with proven activity are produced by non-specific conjugation to lysine residues and to some degree consist of an undesirable heterogeneous mixture of ADCs containing drug molecules with high DAR.”

Mersana Therapeutics developed its Fleximer platform, at least in part, to address the desire to raise the DAR for increased efficacy while limiting immunogenicity. And the polymer is designed to be biodegradable, helping to improve safety. Using this platform, the company can achieve DAR of 15 to 20, a significant improvement over the three to four DAR of earlier generation ADCs.

In April, at the annual meeting of the American Association for Cancer Research, Mersana announced preclinical results from its XMT-1536 program in patient-derived xenograft models of non-small cell lung cancer (NSCLC) and ovarian cancer. With XMT-1536, 15 auristatin conjugates are positioned to a humanized antibody against the sodium-dependent phosphate transport protein β3 (NaPi2b), which is highly expressed in the tumors. Citing durable tumor regression as well as its tolerability and pharmacokinetic profiles, Mersana’s chief medical officer, Donald Bergstrom, suggested the company was advancing the program into IND-enabling studies.

More recently, in a collabora-
tion with Takeda, Mersana also announced the FDA had cleared the way for the company to begin Phase 1 studies on its anti-HER2 conjugate XMT-1222, which carries 12 molecules of auristatin. The Seattle Genetics is responsible for the FDA-approved antibody-drug conjugates currently on the market: CD30-directed ADCs for Hodgkin’s lymphoma and systemic anaplastic large cell lymphoma.

goal, says the company, is to extend HER2-targeted therapy beyond HER2-positive patient populations into those with lower HER2 expres-
sion, in cancers such as advanced breast cancer and NSCLC.

For its part, Sutro Biopharma has taken a synthetic approach to improving ADC homogeneity, incorporating non-natural amino acids at key positions within the targeting antibody to ensure precisely positioned drug linkage and consistent DAR. At the recent American Society of Hematol-
ogy annual meeting, the company presented scientific data from investiga-
tional ADCs targeting CD74 for cell-killing efficacy against a variety of B cell malignancies.

The compounds also demonstrated tumor growth suppression in mouse mod-
els of non-Hodgkin’s lymphoma and multiple myeloma.

Synaffix takes a different approach to ensuring consistency in DAR, focusing its attention on the glycoprofile of antibodies rather than their amino acid sequences. Specifically, the company uses its GlycoConnect platform to enzymatically clip the two glycans that occur naturally on all antibodies and then modify the remaining glycostructure with a second enzyme, preparing it for site-specific stable conjugation with the ADC payload using metal-free click chemistry.

In July, the company announced it had generated ADCs with signifi-
cantly improved therapeutic indicies over the FDA-approved ADCs Adcetris and Kadcyla using Gly-
coConnect and its linker platform HydraSpace.

“What is exciting about our tech-
ology is that we can now consis-
tently synthesize in preclinical models of liquid and solid tumors that if we connect the same anti-
body and payload from each com-
mmercially available ADC product using our proprietary technology, we are able to increase the efficacy of the drug as well as its safety and tolerability,” said Synaffix’s chief scientific officer, Floris van Delft in an announcement.

More recently, the company entered into a commercial license agreement with ADC Therapeutics
The move was just the latest by Takeda, which in September also announced it had signed a research collaboration deal with Affilogic to develop central nervous system therapies. Affilogic has an antibody mimetic platform it dubs Nanofinits—polypeptides that are about one-twentieth the size of antibodies and are easily produced in biofermenters. Like Humabodies, Nanofinits were designed not only to be used alone, but also to be conjugated to other molecules such as drugs or nanoparticles, or to be assembled as multimers, offering the option for multiple specificities and multivalences.

Among its 42 applications of Nanofinit technology, the company has several partnered and "The independent function of the antibody is not always beneficial and complementary to ADC efficacy, especially when Ab binding is sufficient to produce a cytotoxic effect. The Ab's independent effector functions could lead to increased toxicity, reduced tumour localization and internalization of the ADC.”

Nikolaos Diamantis and Uda Banerji of the Institute of Cancer Research

independent candidates in its pipeline, all in preclinical development presently, across therapeutic indications ranging from oncology to autoimmunity to infectious disease. The Takeda agreement will see Affilogic receive upfront payments and research funding with options on downstream development and sales milestone payments in exchange for global commercialization rights.

Avacta Group, meanwhile, has developed a variety of research tools and therapeutics with its Affimer platform. Affimers are small protein scaffolds derived from the cystatin protein fold, and can function both at the surface of and within cells.

Therapeutically, Avacta is focusing on checkpoint inhibition, and in September the company announced positive results from its first preclinical animal studies of its PD-L1 inhibitor. In a pharmacokinetics

ANTIBODY CONTINUES ON PAGE 22
In 2014, the FDA Approved Amgen’s blinatumomab (BlinCyto) for treatment of relapsed/refractory acute lymphoblastic leukemia. Blinatumomab was the first approved compound from a new category of immunotherapy known as a bispecific T cell engager, or BiTE.

Comprised of two single-chain Fv modules, blinatumomab binds to CD3 on the surface of B cells with one arm, and then recruits and activates T cells, which triggers apoptosis via granzymes and perforins. The BiTE platform also formed the basis of solitomab, which recruits CD3+ T cells to EpCAM+ cancer cells and is currently in preclinical study in uterine and ovarian cancers. That collaboration with the University of Minnesota generated a bispecific molecule (161533 TriKE) that targeted CD16 on NK cells and CD33 on myeloid cells for the treatment of acute myeloid leukemia (AML). Not only did 1633 BiKE stimulate NK cells to destroy AML cells, but it also restored NK cell function that had previously been inhibited in patients with myelodysplastic syndrome, a precursor to AML.

“Others have taken the principal behind BiTEs, but rather than tether cancer cells to cytotoxic T cells, they have instead targeted natural killer (NK) cells with constructs known as bispecific killer cell engagers (BiKEs) and more recently, TriKEs (a trispecific variation on the theme),” Danile Tarsitano, director and chief scientific officer at Avidity’s Alessandro Santin and colleagues noted last year, exposure of solitomab made EpCAM+ cell lines sensitive to T cell-mediated killing and significantly reduced the number of viable ovarian tumor cells in ascites.

“The widespread expression and expression localization of EpCAM in ovarian cancer cells, combined with its negative expression in mesothelial cell types in the abdominal cavity, suggests that this protein could represent an accessible tumor target antigen for both intravenous and intraperitoneal antibody/BiTE-based therapies,” the authors enthused in Cancer. “Consistent with this view, a Phase 1 study of EpCAM/CD3-bispecific antibody (MT110) in patients harboring advanced tumors is currently ongoing.”

Others have taken the principal behind BiTEs, but rather than tether cancer cells to cytotoxic T cells, they have instead targeted natural killer (NK) cells with constructs known as bispecific killer cell engagers (BiKEs) and more recently, TriKEs (a trispecific variation on the theme).

Daniel Tarsitano and colleagues at the University of Minnesota generated a bispecific molecule (161533 BiKE) that targeted CD16 on NK cells and CD33 on myeloid cells for the treatment of acute myeloid leukemia (AML). Not only did 1633 BiKE stimulate NK cells to destroy AML cells, but it also restored NK cell function that had previously been inhibited in patients with myelodysplastic syndrome, a precursor to AML.

However, these researchers then added a third component—crosslinked human IL-15—to drive NK cell expansion. The resulting molecule (161533 TriKE) was superior to its predecessor BiKE in almost every way, including enhanced cancer cell killing, NK cell proliferation and survival, and significantly reduced tumor load in mice engrafted with human CD3+ myeloid cells.

“TriKEs can be generated with different specificities, they provide the option to re-target NK cells in accordance with the emergence of tumor-associated antigens during tumor escape and immunoeediting, which could impede the long-term success of cancer therapies,” commented Szuin Szuin Tay and colleagues at the University of New South Wales and University of Sydney in a recent issue of Human Vaccines and Immunotherapeutics.

“The TriKE platform not only provides options to target different receptors, or novel tumor ligands, but also provides a way to explore new targeting strategies based upon newly discovered molecules reasonably rapidly,” the authors enthused.

Recently, Christoph Rader and colleagues at The Scripps Research Institute and the U.S. National Institutes of Health looked to make bispecific antibodies more modular in design, commoditizing the actual antibody component and adding variability to the T cell binding arm via an array of small molecules.

As they described recently in the Journal of Biological Chemistry, the researchers utilized the DART (dual-affinity re-targeting) format, which involves two peptide chains linked by a disulfide bond (diabody). Each chain contains one of the two variable light and heavy domains that form the antigen and hapten binding site. They then chemically programmed the complexes with folate derivatives that would target the folate receptor (FOLR1) on ovarian cancer cells.

Not only did the diabodies bind both CD3+ and FOLR1+ individually, but the researchers used flow cytometry to show the diabodies could crosslink CD3+ and FOLR1+ cells. The diabodies also exhibited strong cytotoxic effect on ovarian cancer cells both in vitro and in vivo in xenotransplanted mice. Treated mice also showed reduced tumor burden without signs of toxicity.

“A key advantage of chemically programmed antibodies and [bispecific antibodies] is their generic design that not only enables [one] to confine lead optimization to the small-molecule component but also permits targeting a virtually unlimited number and variety of antigens with a single protein,” the authors wrote.

Thus, they concluded, “our chemically programmable DARTs afford a versatile plug-and-play platform with broad utility in cancer immunotherapy.”

It seems that as the number of potential targets increases, so too do the methods with which to tether variability to the T cell binding arm and on an as-needed basis.

**AMBbody**

Continued from page 21, the study, the anti-PD-1 Affimer fused to an Fc domain demonstrated good in vivo half-life and was well tolerated at clinically relevant concentrations. In a second, efficacy study in a syngeneic mouse model, the inhibitor was able to significantly reduce tumor growth with no observed adverse events.

“The results demonstrate that Affimer molecules possess good in vivo drug-like properties in terms of efficacy, serum half-life and tolerability, which is a hugely important milestone in the development and de-risking of the technology as a therapeutic platform,” commented Alastair Smith, Avacta Group chief executive, in the announcement.

“We are very encouraged by these initial, positive results and will continue to focus on developing both our internal and partnered therapeutic programs towards clinical validation.”

**Bottom line**

Thus, as larger pharmas and biotechs fight in the biosimilar market to simply reproduce the success of first-generation antibody therapies and others continue to ply the full antibody trade with next-generation therapeutics, several other players are applying the lessons of the biopharma market to evolve the art form.

The success of products like Adcetris, Kadcyla and BlinCyto will undoubtedly impact how much drug and human effort people will put into this research in the years to come, and will provide lessons of their own.
Melbourne Hospital and Peter MacCallum Cancer. Jayesh Desai, a medical oncologist at The Royal

tivity as a Phase 1/2 study combin-

ing linifilumab and Opdivo (nivolumab) in patients with advanced platinum refractory squamous cell carcinoma of the head and neck (SCCHN) was reported recently by Bristol-Myers Squibb and Innate Pharma SA. The objective response rate (ORR) among 29 evaluable patients with SCCHN was 24 percent, and 17 percent of the evaluable patients showed deep responses with tumor burden reduction of more than 80 percent. The analysis also included exploratory biomarker analyses of patient response by level of PD-L1 expression; early signals of enhanced clinical benefit were seen in PD-L1-positive tumors, with an ORR of 41 percent in patients with >1% PD-L1 expression. The data from this analysis are the first demonstrating potential efficacy of combining an anti-

KIR antibody with an anti-PD-1 therapy.

BGB-A317 shows activity in multiple cancer types

WALTHAM, Mass. — Clinical-stage biopharmaceutical company BeliGene Ltd. presented updated clinical data on its ongoing Phase 1 study of BGB-A317 in patients with advanced solid tumors at last month’s Society for Immunotherapy of Cancer 31st Annual Meeting. The drug is an investigational humanized monoclonal antibody against PD-1 and is being evaluated in a multicenter, open-label trial to determine its safety, tolerability, pharmacokinetics and antitumor activity in patients with advanced solid tumors. Of the 99 evaluable patients, there were 15 confirmed partial responses across nine cancer types and 23 cases of stable disease.

“We continue to see promising antitumor activity with BGB-A317 and a safety profile that is consistent with this class of molecules,” said Dr. Jayesh Desai, a medical oncologist at The Royal Melbourne Hospital and Peter MacCallum Cancer Centre in Melbourne, Australia, and coordinating principal investigator of the study.

Research shows promising results on the use of CRS-207

BY JENNIFER CLIFFORD

BERKELEY, Calif. — Aduro Biotech Inc. recently announced preliminary data from an ongoing Phase 1 clinical trial on the safety and efficacy of its novel immunotherapy, CRS-207, in unresectable malignant pleural mesothelioma in a poster presentation at the Annual Meeting of the Society for Immunotherapy of Cancer in National Harbor, Md. The findings reported were from the second cohort of patients using CRS-207 in combination with standard-of-care chemotherapy and immune-modulating doses of cyclophosphamide as a first-line treatment.

As of October 2016, of the 22 patients in that second cohort, 82 percent of patients had disease control, with 55 percent of patients achieving a partial response and 27 percent with stable disease. Also reported was tumor shrinkage observed in 12 patients, with an overall response rate (ORR) of 77 percent, 36 percent responding after two doses of immunomodulatory doses of cyclophosphamide combined with CRS-207, but prior to initiation of standard-of-care chemotherapy. No treatment-related serious adverse events or unexpected toxicities were observed. Additional analysis of paired tumor biopsies obtained from two patients showed a marked infiltration of immune effector cells into the tumor microenvi-

ronment following two doses of CRS-207, and post-therapeutic changes included an increase in CD8+ cytotoxic T cells as well as an increase in other immune cell types that are thought to be essential for effective immunotherapy, including dendritic cells and natural killer cells, correlating with other positive clinical outcome.

“The data from the second cohort, which is a patient popu-

lation with more advanced disease compared to the first cohort, demonstrate that the addition of immunomodulatory doses of cyclophosphamide, which has been shown to inhibit negative regulatory T cell populations, to the combination of CRS-207 and chemotherapy results in encouraging disease control and toler-

ability for patients with meso-

thelioma,” commented Dr. Dirk G. Brockstedt, executive vice president of research and develop-

ment of Aduro. “Importantly, we believe these data, together with the results from the first cohort, support further investigation of CRS-207 in mesothelioma, and we intend to initiate a Phase 2 study of CRS-207 in combination with an anti-PD-1 therapy as an immune-modula-

tor in patients with mesothelioma who have failed at least one prior therapy.”

Aduro has had an interest in mesothelioma for some time, the basis for this research stemming from work done at Johns Hopkins.

New disease findings and old clinical trials

Study supports using amyloid inhibitors to treat Alzheimer’s disease

BY ILENE SCHNEIDER

FRAMINGHAM, Mass. — Alzheon Inc., a biopharmaceutical company focused on treatments for neurodegenerative and neuropsychiatric disorders, recently published the first report to associate efficacy of an amyloid-targeted drug with the number of APOE4 alleles in individuals possessing in The Journal of the Prevention of Alzheimer’s Disease.

The results could lead to a novel precision medicine approach in Alzheimer’s disease (AD) drug development, the authors claimed. Pivotal studies of ALZ-801, an oral produg of trampoxin, to target AD patients who are APOE4 carriers, will be initiated in 2017.

According to Dr. Susan Abushakra, chief medical officer of Alzheon, continued on page 25.

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PS promise in cancer

Peregrine preclinical studies support a combo approach being studied in clinical trials

BY LORI LESKO

TUSTIN, Calif. — Aimed at finding the right formula to fight can-

cer, West Coast biopharmaceutical Peregrine Pharmaceuticals Inc. has presented positive data from multiple new preclinical studies of the company’s phosphatidylserine (PS)-targeting antibodies in a poster to the Society for Immunotherapy of Cancer (STIC) in National Harbor, Md. The data highlight research showing PS-targeting antibodies, similar to bavituximab, synergize with checkpoint inhibitors and radiation to improve antitumor activity in various animal tumor models. Initial results from Peregrine’s ongoing collaboration with Memorial Sloan Kettering Cancer Center (MSK) researchers were presented by Sadna Budhu at STIC. A team of MSK researchers headed by cancer immunotherapy leader Taha Merghoub and Dr. Jedd D. Wolchok evaluated the effects of combining PS-targeting, anti-PD-1 and radiation therapies.

“Based on these study results, we believe that the target-

ing of PS is having meaningful activity within the tumor microenvironment in the B16 melanoma model,” Wolchok stated in a news release. “It appears that this activity creates a more immune-active environment in which other treat-

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Novel antiepileptic for Dravet syndrome

New extended release formulation and preclinical data set stage for Phase 1b Trial to start in mid-2017

BY DDNEWS STAFF
MIAMI BEACH, Fla. – Biscayne Pharmaceuticals Inc. in October reported that a new scientific publication shows that lead compound BIS-001 can eliminate all seizures in the majority of animals in models of the type of epilepsy known as Dravet syndrome. BIS-001 is a clinical stage, highly potent agent with a novel mechanism of action that is a synthetic form of huperzine A, an extract of a traditional Chinese medicine. Biscayne is initially developing BIS-001 for the treatment of children with Dravet syndrome and for adults with complex partial seizures.

The new studies assessed BIS-001 in mice who have the same SCN1A mutations seen in human Dravet syndrome and are subject to similar severe seizures. The study was conducted in the Emory University Laboratory of Dr. Andrew Escayg, who is a leading expert in the human and mouse genetics of neurological diseases. In these studies, BIS-001 completely eliminated seizures in the majority of treated animals at doses expected to be well tolerated and achievable in patients with a new extended-release formulation of BIS-001.

Importantly, the effects of BIS-001 were sustained over time, with high levels of antiseizure activity maintained during repeat dosing for up to 21 days, with no evidence of the tachyphylaxis, or diminishing effect, that is seen with other antiepileptic drugs. BIS-001 appeared to be well tolerated in these animals.

“BIS-001 demonstrated a high level of efficacy in these models of extremely hard-to-treat epilepsy, eliminating all seizures in most animals and maintaining efficacy over repeat administration, at dose levels we are optimistic will be effective and well tolerated in patients with our new extended-release formulation,” said Dr. Stephen Collins, president and CEO of Biscayne Pharmaceuticals. “We are encouraged by these promising results in a model of devastating childhood epilepsy as we prepare to initiate a Phase 1b clinical trial of BIS-001 in another population with difficult-to-treat seizures—adults with refractory complex partial epilepsy.”

The active ingredient of BIS-001 is huperzine A, an acetylcholinesterase (AChE) inhibitor that has a long history of safe use in Chinese medicine, Collins continued. “It also has exhibited the cognition-enhancing properties seen with some other AChE drugs, but has demonstrated much better neuronal safety and systemic tolerability and safety than currently available agents. We will be assessing whether BIS-001 supports improved cognition in epilepsy patients, and at the least, we expect it to be devoid of the detrimental effects on cognition seen with many existing antiepileptic drugs. We are eager to test BIS-001 in a variety of conditions, given the high unmet therapeutic need that exists across the spectrum of seizure disorders.”

Biscayne expects to advance BIS-001 into a Phase 1b study in adults in mid-2017. The proof-of-concept study will evaluate novel bavituximab combinations in glioblastoma, head-and-neck cancer and hepatocellular cancer, a disease including an immunotherapy combination.”

"While these trials are not direct follow-ups to the preclinical work presented at SITC, they do seek to build upon the scientific support that Peregrine is generating for combinational cancer treatments featuring its PS-targeting antibodies,” he added. According to Hutchins, “a second study, conducted by Peregrine, evaluated the effects of combining PS-targeting, anti-PD-1 and anti-LAG-3 therapies in the E935 triple negative breast cancer model. Initial findings from this study were previously reported and demonstrated that triple combination treatments significantly increased complete tumor regressions, whereas the most promising dosing regimens in the anti-PD-1 and anti-LAG3 combination treatment arm that had a complete regression.”

The study was designed to include eight separate arms (control and treatment) with 15 subjects in each arm (10 in the main study and five for analysis of the tumor microenvironment), Hutchins explained. As such, this study evaluated a total of 120 mice. The data highlighted in this release compared the 15 mice in the triple combination arm, with the 15 mice in the anti-PD-1/anti-LAG3 combination arm.

Peregrine’s next step is to “continue to conduct targeted preclinical research aimed at generating additional data to support the potential role of PS targeting antibodies as part of anti-PD-1/PD-L1 combination cancer treatments,” said Dr. Steven Schachter, professor of neurology at Harvard Medical School, a scientific co-founder of Biscayne and a co-author of the new study, and commented, “We are eager to test BIS-001 in clinical trials to see if the dramatic elimination of BIS-001 seizures observed in these animals can be replicated in patients, who are in great need of better treatment options.”

Peregrine continued from page 23
Jeff T. Hutchins, Peregrine’s vice president of preclinical research, told DDNews, “Peregrine’s clinical development strategy for bavituximab currently focuses on small, early-stage, proof-of-concept trials evaluating the drug in combination with other cancer treatments. This approach includes the recently announced grants awarded by the National Comprehensive Cancer Network to support three different clinical trials of bavituximab in glioblastoma, head-and-neck cancer and hepatocellular cancer, including an immunotherapy combination.”

“While these trials are not direct follow-ups to the preclinical work presented at SITC, they do seek to build upon the scientific support that Peregrine is generating for combinational cancer treatments featuring its PS-targeting antibodies,” he added. According to Hutchins, “a second study, conducted by Peregrine, evaluated the effects of combining PS-targeting, anti-PD-1 and anti-LAG-3 therapies in the E935 triple negative breast cancer model. Initial findings from this study were previously reported and demonstrated that triple combination treatments significantly increased complete tumor regressions, whereas the most promising dosing regimens in the anti-PD-1 and anti-LAG3 combination treatment arm that had a complete regression.”

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**CLINICAL TRIALS**

### ADURO

Continued from page 23

University regarding GVAX. GVAX is a therapeutic cancer vaccine being investigated for its use in prednisolone-based therapy in patients with pancreatic cancer, and Aduro is currently evaluating CRS-207 and GVAX Pancreas in combination with the checkpoint inhibitor atezolizumab, in the STELLAR trial, a Phase 2 randomized controlled trial in patients with metastatic pancreatic cancer. “This has been studied for decades, Brockstedt stated in an interview with DDNews regarding the use of the body’s innate immunity to trigger T cell response. “The first step was to develop a strain that was safe for patients.” He added that over 100 human subjects have treated specifically using Listeria, with most of the reactions being infection site-related reactions of BIS-001 toxicity.

The initial cohort in the CRS-207 study started with 16 patients, but with promising results was expanded to 36 patients. While the first cohort experienced a pure combina-
of Alzheimer’s, “there is a lot of evidence supporting the important role of amyloid burden in the disease. Most genetic mutations that lead to familial AD involve the amyloid precursor protein (APP) gene leading to increased produc- tion of amyloid. The few genetic mutations that are protective from AD also involve the APP gene and lead to less production of beta amyloid. The APOE4 (apolipopro- tein E) allele, the strongest risk fac- tor for AD, plays an important role in beta amyloid metabolism and is associated with more beta amyloid production and deposition.”

Abushakra explained that there is a strong rationale for drugs that target and inhibit amyloid aggre- gation and neurotoxicity, which are hallmarks of Alzheimer’s disease. She believes that a greater understanding has now emerged about the reasons that the first generation of disease modifica- tion trials with amyloid-targeted agents, who were completed before the availability of amyloid imaging, have failed.

Most first-generation studies enrolled patients based only on a clinical diagnosis of AD, without amyloid imaging,” she said. “We now know that a high percentage of patients in these studies do not actually have amyloid, especially the APOE4 non-carriers. Therefore, amyloid-targeted drugs do not have a chance to show benefit in such studies.”

The fact that amyloid drugs have such a large body of clinical evidence is being “missed” as an asset, according to Abushakra. Instead of “closing the books” on failed studies with amyloid-targeted drugs for Alzheimer’s treatment, researchers are drawing insights from new disease find- ings to guide further refined studies with still-promising drugs in more tar- geted populations. Alzheimer’s work with analyzing the Phase 3 data for trimproaturam is an example of leveraging past clinical studies to identify and accelerate new treat- ment opportunities with an oral, amyloid-targeted drug candidate, which is an oral drug, not an injectable antibody, and its active molecule, trimproaturam, did not show increased risk of ARIA in clinical studies. Alzheimer’s patients who are APOE4 carriers are more responsive to amyloid-targeted medica- tions because they have a higher load of vascular amyloid com- pared to non-APOE4 carriers, according to Abushakra. “Furthermore, APOE4 homozygotes have 95-percent likelihood of having amyloid pathology and of showing potential efficacy with an amyloid-targeted drug,” she said. Alzheon has a very strong clini- cal dataset in APOE4 homozyg- otes, a biologically and clinically relevant population at highest risk for development of AD, highest beta amyloid load and fastest deter- mination of significant amyloid burden, according to Abushakra.

As she explained, “The mag- nitude of the effect that we have seen, particularly in the mild AD population, suggests potential for significant delay of disease progression and even cognitive improvement. To date, no clini- cal trials have been conducted in APOE4 homozy- gotes. Alzheon is trailblazing in the design of the planned studies with ALZ-801. The studies with ALZ-801 will utilize a ‘precision medicine’ approach, where the study population will be based on APOE genotype.”

DATA
CONTINUED FROM PAGE 1
at treatment initiation.”

The pooled analysis looked at Olyve’s efficacy in terms of disease progression in patients grouped by their GAP (gender, age, physiolo- gy) stage; at baseline, 506 patients were at GAP stage I, and 580 were at GAP stage II/III. Patients saw similar reductions in disease pro- gression with Olyve compared to placebo regardless of GAP stage. Treatment effect remained con- stant for the two GAP groups when progression was measured as an absolute forced vital capacity (FVC) decline ≥20 percent predicted or death over 52 weeks.

Another post-hoc pooled analysis of the trials examined the effect of treatment on disease progression based on patients’ baseline com- posite physiologic index (CPI), which reflects disease severity through spirometric volumes and measures of gas transfer without radiolabeled inert gases. The analyses looked at patients with regards to basal CPI of ≤25 versus >25, and ≤55 versus >55, with a higher CPI score associated with a worse prognosis. At baseline, 462 patients had CPI ≤25 and 538 had CPI >25; 829 patients had CPI ≤55 and 231 had CPI >55.

With the baseline CPI thresh- old of 45, treatment effects were comparable based on the time to absolute decline in FVC ≥20 percent predicted or death over 52 weeks. No significant dif- ferences in treatment effects were seen when a baseline CPI threshold of 55 was used to define subgroups for time to absolute decline in FVC ≥25 percent or death for time to absolute decline in FVC ≥20 percent or death.

In September, the company shared study results from its Phase 3 CanoTinA-asthma trial demon- strating that adding tiotropium Respimat, an inhaled long-acting anticholinergic bronchodilator, to maintenance asthma therapy in children ages 6 to 12 significantly improved lung function. The trial consisted of children who were already using an inhaled corticois- troid (ICS) or an ICS together with other maintenance therapy.

A pooled analysis from four studies—VivaTinA-asthma, RubaTinA- asthma, PensieTinA-asthma and CanoTinA-asthma—demonstrated that adding tiotropium Respimat to maintenance therapy for children aged 6 to 17 years has a comparable safety profile to placebo. In chil- dren ages 6 to 10, adding the thepa- peutic to maintenance therapy saw a safety profile consistent with that seen in older children and adults. At the same time, Boehringer Ingelheim shared two sets of news for patients with COPD. The company released the first results from its Phase 3b PHYSACTO trial, which showed that Stolido Respimat, together with exercise training, helped COPD patients walk for longer periods of time compared to those on placebo. In fact, participants in that trial arm saw their exercise capacity increase by 4.58 percent compared to those on placebo. Even without exer- cise training, participants in the tiotropium +olodaterol Respimat arm saw significant improvement in their exercise capacity, to the tune of a 29.2-percent increase in shuttle walk duration compared to placebo.

In a post-hoc subanalysis of its WISDOM study, Boehringer Ingel- heim found that only four out of 100 people with COPD and a his- tory of frequent exacerbations and raised eosinophil levels are likely to see further benefit from adding ICS to Spiriva (tiotropium) and a long-acting beta-agonist (LABA) in terms of reducing their exacer- bation risk.

COPD exacerbations are a sig- nificant contributor to the disease’s impact. The Global Initiative for Chronic Obstructive Lung Disease (GOLD), a collaboration between the World Health Organization and the National Institutes of Health, recommends the use of ICS-con- taining therapy only in COPD patients with severe to very severe lung function impairment and/or who are at high risk of exacerbations or who have had a hospital- ization in the past 12 months (the WIS- DOM patient population). ICS are commonly used outside of GOLD treatment recommendations together with bronchodilators, such as tiotropium and LABAs, to treat COPD.

New results from the WISDOM study indicate that using ICS as part of a triple therapy regimen in COPD maintenance treatment reduces the likelihood of an exac- erbation for a smaller number of people than previously thought. It challenges our current understand- ing of the appropriate use of ICS in COPD maintenance treatment,” said Prof. Peter Calverley, professor of pulmonary medicine at the Univer- sity of Liverpool, who led the study inves- tigating. “These study results add important information to a debate that has potentially wide-ranging implications for the future treat- ment of people with COPD.”

Boehringer Ingelheim’s cancer efforts have included a focus on team-ups for clinical development or trials. Among other announce- ments, the company shared news in October that it would be joining The Leukemia & Lymphoma Soci- ety (LLS) in a first-of-its-kind col- laborative trial program to advance treat- ments for acute myeloid leuke- mia (AML) patients: the Beat AML Master Trial. This undertaking will assess investigational medicines from a number of biopharmaceuti- cal companies and enroll newly diagnosed patients, which will be assigned to treatment arms based on their genomic analysis. Of those treatment arms, one will include BI 836858, Boehringer Ingelheim’s investigational anti-CD33 mono- clonal antibody.

The Beat AML Master Trial is “a unique opportunity to put the interests of a partic- ularly underserved patient population front and center by bringing multiple biopharmaceutical companies with investigational medi- cines targeting AML together,” Dr. Martina Flammer, vice president of Clinical Development & Medical Affairs Specialty Care at Boehringer Ingelheim, remarked. “Boehringer Ingelheim is proud to join other leading experts and medical cen- ters to take part in this pioneering initiative.”

Boehringer Ingelheim kicked off another cancer-focused partner- ship around the same time, this one a strategic collaboration with the Sarah Cannon Research Institute, the research arm of Sarah Cannon, the global cancer institute of HCA. The goal is to bring innovative cancer treatments to patients with unmet medical needs, specifically novel immune-oncology therapies. Through this joint clinical develop- ment program, the two organizations will study BI 754591 (anti- PD-L1; LAG-3) monoclonal antibodies from Boehr-inger Ingelheim indicated for the combination treatment of multiple cancers, including non-small-cell lung cancer. Through pre- liminary findings, the collaboration could expand to include other areas or targets of interest. –

CLINICAL TRIALS
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Kettering Cancer Center, Oregon Health & Science University, Dana-Farber Cancer Institute and Massachusetts General. It is anticip- ated that the first patients will be enrolled this month, with six additional sites prepared to start enrolling patients in April 2017. The eventual goal is to expand this effort to between 15 and 20 sites, with an additional 600 patients and 500 patients. Other collabora- tors in the Beat AML Master Trial include Foundation Medicine, INC (Cambridge, MA), Pfizer, Mylan, Alexion, Celgene and Gilead.

“This is a unique opportunity to put the interests of a particu- larly underserved patient popula- tion front and center by bringing multiple biopharmaceutical companies with investigational medi- cines targeting AML together,” Dr. Martina Flammer, vice president of Clinical Development & Medical Affairs Specialty Care at Boehringer Ingelheim, remarked. “Boehringer Ingelheim is proud to join other leading experts and medical cen- ters to take part in this pioneering initiative.”

Boehringer Ingelheim kicked off another cancer-focused partner- ship around the same time, this one a strategic collaboration with the Sarah Cannon Research Institute, the research arm of Sarah Cannon, the global cancer institute of HCA. The goal is to bring innovative cancer treatments to patients with unmet medical needs, specifically novel immune-oncology therapies. Through this joint clinical develop- ment program, the two organizations will study BI 754591 (anti- PD-L1; LAG-3) monoclonal antibodies from Boehr-inger Ingelheim indicated for the combination treatment of multiple cancers, including non-small-cell lung cancer. Through pre- liminary findings, the collaboration could expand to include other areas or targets of interest. –

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NSCLC stratification

Biodex’s VeriStrat proves capable of identifying patients who will respond to EGFR-TKI therapy

BY KELSEY KAUSTINEN

BOULDER, Colo.—This year’sIASLC Multidisciplinary Symposium in Thoracic Oncology hosted by the International Association for the Study of Lung Cancer featured a number of presenters, including Biodesix, which shared recent data regarding its VeriStrat test and its use in identifying patient subsets in lung cancer. The Symposium was held Sept. 22-24 in Chicago.

Biodesix’s presentation consisted of results of subset analyses of its TIGER-X and TIGER-2 clinical trials demonstrating that VeriStrat can stratify Tyrosine Kinase Inhibitor-Mutated (TKI-M) patients with previously treated, advanced non-small cell lung cancer (NSCLC) who are more or less likely to experience longer progression-free survival (PFS) when treated with a third-generation EGFR-TKI therapy like erlotinib. An individual’s EGFR mutation status is known to highlight NSCLC patients who see better outcomes when treated with EGFR-TKI therapy compared to standard platinum-doublet therapy in a front-line setting. There is, however, a subset of patients who will present with de novo resistance, and acquired resistance is expected for all patients. In up to 60 percent of patients, the EGFR Tyrosine Kinase Inhibitor mutation is the mechanism of resistance at progression.

The VeriStrat test is a predictive, prognostic blood-based proteomic test for patients with advanced NSCLC who are treated with erlotinib. Biodesix reported in a press release that its patients with VeriStrat test results had a median PFS of 127 days. PFS was analyzed for patients with ECOG status of 0 (63 patients; median 169 days) or 1 (169 patients; 125 days) and was found to have a hazard ratio of 0.85.

In one of those presentations, “Examination of Diurnal and Daily Variation of the Multi-biomarker Disease Activity (MBDA) Score in RA to Establish a Minimal Importantly Difference,” the research evaluated the biological variability in Vectra DA scores over a 24-hour period and day-to-day in 28 patients suffering from rheumatoid arthritis.

Epic uncovers prostate cancer biomarker

Liquid biopsy test matches patients to metastatic prostate cancer treatment

BY LORELEI LESKO

SAN DIEGO—Biotech company Epic Sciences’ focus on circulating tumor cells (CTCs) will not only advance the clinical use of liquid biopsies and improve how metastatic cancer is treated, but has also identified a unique CTC biomarker in patients with metastatic prostate cancer who respond to PARP inhibitors.

Epic uncovers prostate cancer biomarker

Liquid biopsy test matches patients to metastatic prostate cancer treatment
VECTRA CONTINUED FROM PAGE 26
From the U.S. Medicare claims database of patients with RA (approximately 17,000 patients), researchers examined the relationship between the Vectra DA score and the risk of developing infections requiring hospitalization, myocardial infarction (MI) and a composite of coronary heart disease (CHD), including percutaneous coronary intervention and coronary artery bypass graft. The results showed that high Vectra DA scores were associated with an increased risk for infections requiring hospitalization, MI, CHD and CHD events. These findings indicate that the use of the Vectra DA score to risk-stratify patients for these serious adverse events may help clinicians identify those at highest risk.

The other poster was titled “Multi-Biomarker Disease Activity (MBDA) Score and Prediction of Radiographic Progression in a Randomized Study of Patients with Early RA Treated with Methotrexate Alone or with Adalimumab.” The objectives of this study were to evaluate 180 early RA patients from the OPERA trial for associations between the baseline Vectra DA score and 12-month radiographic outcomes, and to assess the value of adding the Vectra DA score to the anticyclic citrullinated peptide (anti-CCP) status for predicting radiographic progression. The results showed that a high baseline Vectra DA score was a strong, independent predictor of radiographic progression and it added value to anti-CCP status.

“Crescendo is pioneering a personalized medicine approach for autoimmune disorders and is committed to helping all patients with rheumatoid arthritis achieve their treatment goals,” Dr. Elena Hitraya, chief medical officer of Crescendo. "We are excited about the new data being presented at ACR that advances the science for Vectra DA and will help rheumatologists improve care for their patients with rheumatoid arthritis.”

“Crescendo is pioneering a personalized medicine approach for autoimmune disorders and is committed to helping all patients with rheumatoid arthritis achieve their treatment goals.” Dr. Elena Hitraya, chief medical officer of Crescendo

The other physician/treatment-focused poster was titled “Predicting Flare and Sustained Clinical Remission After Adalimumab Withdrawal Using the Multi-Biomarker Disease Activity (MBDA) Score.” This study evaluated the Vectra DA score as a predictor of flare or sustained clinical remission after discontinuation of adalimumab in patients with established RA from the HONOR study. Vectra DA scores were measured at adalimumab discontinuation, and the ability of Vectra DA to predict flare or remission was assessed at six months and one year. The findings suggest that the Vectra DA score could predict flare and biologic-free remission in patients in stable remission undergoing adalimumab withdrawal while maintaining methotrexate treatment. The results point to the potential clinical utility of Vectra DA for guiding treatment decisions in patients with RA.

As noted earlier, the other two presentations detailed studies regarding the utility of Vectra DA in predicting the occurrence of heart disease and other infections among RA patients, as well as the longitudinal relationship with radiographic progression. The first, “Biomarker-Related Risk for Myocardial Infarction and Serious Infections in Patients with Rheumatoid Arthritis: A Population-Based Study,” evaluated the utility of Vectra DA in assessing the risk of cardiovascular outcomes and serious infections in a large
HTG and Merck KGaA enter CDx agreement

TUCSON, Ariz. & DARMSTADT, Germany—HTG Molecular Diagnostics Inc., a provider of instrumentation and reagents for molecular profiling applications, and pharma company Merck KGaA of Darmstadt, Germany, have entered a broad companion diagnostics master agreement related to diffuse large B cell lymphoma (DLBCL). The initial development program agreement utilizes the HTG EdgeSeq DLBCL Cell of Origin assay in the Merck KGaA program focused on MYC and a selective and irreversible inhibitor of Bruton’s tyrosine kinase (BTK). “We are honored to be chosen as the diagnostic development partner for Merck KGaA’s BTK program and our team is now focused on the near-term milestones. Additionally, having a master companion diagnostic agreement paves the way for additional development collaborations,” stated TJ Johnson, HTG’s president and CEO. “We have worked very hard to establish the organizational capabilities to support the development, regulatory filing, and commercialization of companion diagnostics demonstrated in the recently CE/IVD marking of HTG’s DLBCL cell of origin assay.”

Headquartered in Arizona, HTG’s mission is to “empower precision medicine at the local level.” In 2013, the company commercialized its HTG Edge instrument platform and a portfolio of RNA assays that leverage HTG’s proprietary nucleic acid protection chemistry. HTG’s product offerings have since expanded to include its HTG EdgeSeq product line, which automates sample and targeted library preparation for next-generation sequencing.

“Impactful therapy and eventually develops genomic instability called homogeneity is believed to be responsible for the second-line treatment of patients with squamous cell carcinoma of the lung. While further validation studies are needed, the VeriStrat test has the potential to be a key component of next generation TKI therapy in squamous NSCLC.”

**BIODESIX CONTINUED FROM PAGE 26**

was 168 days for the VS-G patients vs. 91 days for VP-P patients, and for the second-line cohort, median PFS was 127 days for VS-G patients vs. 45.5 days for VS-P patients. For the third- and higher-lines cohort, median PFS was reported at 165 days for VS-G patients vs. 106 days for VP-P patients. VeriStrat test status versus ECOG performance status was also analyzed. For ECOG status 1 patients, VeriStrat stratified patients by median PFS:153 days for VS-G patients vs. 102 days for VS-P patients. The prognostic ability of this test was noted in a 2014 paper published in *The Lancet Oncology* titled “Predictive Value Of A Pro- teomic Signature In Patients With Non-Small Cell Lung Cancer Treated With Second-Line Erlotinib Or Chemotherapy (PROSE): A Biomarker-Stratified, Randomised Phase 3 Trial.” This work focused on patients with histologically or cytologically confirmed, second-line, stage IIIB or IV NSCLC who were enrolled in 14 centers in Italy. Patients were stratified to receive either erlotinib or chemotherapy, with a primary endpoint of overall survival (OS). All told, 1,421 patients were assigned to receive chemotherapy and 1,451 to receive erlotinib, with 129 (91 percent) and 134 (94 percent), respectively, included in the per-protocol analysis. As noted in the paper’s findings, “86 (68 percent) patients in the chemotherapy group and 66 (72 percent) in the erlotinib group had a proteomic test classification of good. Median overall survival was nine months in the chemotherapy group and 77 months in the erlotinib group. We noted a significant interaction between treatment and proteomic classification. Patients with a proteomic test classification of poor had worse survival on erlotinib than on chemotherapy. There was no significant difference in overall survival between treatments for patients with a proteomic test classification of good.” VeriStrat is proving itself in other types of lung cancer as well. Bio- desix announced on Oct. 5 that new clinical work shows that the test can identify patients with squamous cell carcinoma of the lung who are more likely to see longer PFS and OS with irreversible ErbB family blocker afa- 

“**For patients with advanced squamous cell carcinoma of the lung who have ‘good’ status according to the VeriStrat test, EGRF-TKI therapy remains a relevant option, in addition to the recently approved checkpoint inhibitors for this patient population,”** Dr. Glenwood D. Goss of the University of Ottawa said. “We are honored to be chosen as the diagnostic development partner for Merck KGaA’s BTK program and our team is now focused on the near-term milestones. Additionally, having a master companion diagnostic agreement paves the way for additional development collaborations,” stated TJ Johnson, HTG’s president and CEO. “We have worked very hard to establish the organizational capabilities to support the development, regulatory filing, and commercialization of companion diagnostics demonstrated in the recently CE/IVD marking of HTG’s DLBCL cell of origin assay.”

Here Epic Sciences provides phenotypic imagery showing genomic instability, with cells stained for cytokeratin (red), CD45 (green), DNA (blue) and N-terminus of androgen receptor (purple).}

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Here Epic Sciences provides phenotypic imagery showing genomic instability, with cells stained for cytokeratin (red), CD45 (green), DNA (blue) and N-terminus of androgen receptor (purple).}
INC Research unveils Catalyst Community and Catalyst Site Network at summit

BY MEL J. YEATES

RALEIGH, N.C.—INC Research, a global Phase 1 to 4 contract research organization (CRO), had some extensive participation in the Society for Clinical Research Sites’ (SCRS) 11th Annual Global Site Solutions Summit this October. INC Research thought leaders participated in several sessions to discuss issues that impact the way sites conduct research and recruit patients, while offering strategies to improve collaboration between CROs and sites to more effectively benefit patients.

INC Research began its participation with Dr. Clare Grace, vice president of site and patient access, who participated in the summit’s first plenary session, “Sites Matter: Industry Collaboration.” This explored ongoing transformations affecting sites, including investigator turnover, general public awareness of clinical research, study dashboards, sites payments and standardized contract clauses. On day two of the summit, Grace facilitated a roundtable session around fixing the clinical trial awareness challenge and shared highlights from the recent “Inspiring Hope” iteration, a crowdsourcing event that INC Research and the Center for Information and Study on Clinical Research Participation (CISCRP) co-hosted recently in Boston, which brought together a cross-section of stakeholders across the industry.

“We are excited to once again be participating in the SCRS Global Site Solutions Summit, an event that consistently has been instrumental in bringing sites, CROs and sponsors together to improve how we all work together in clinical research,” said Grace. “The strides we’ve made in recent years to streamline different aspects of the clinical trial process, such as investigator payments, is evidence of this collaboration, but we still have a long way to go. Connecting with sites in such a synergistic environment gives us an opportunity to gain a better understanding of their perspectives and remain mindful of all of the valuable contributions they make in bringing new medicines to market. Without sites, we simply wouldn’t be able to deliver clinical trials.”

The participation at the summit also gave INC a chance to pitch its services. In an effort to strengthen collaborations with clinical INC CONTINUED ON PAGE 31

Strengthening clinical research sites

Bracket acquires CLINapps

WAYNE, Pa.—Mid-November saw Bracket, a clinical trial technology and specialty services provider, announce the strategic acquisition of CLINapps Inc., an international software development and consulting firm that offers a comprehensive supply chain management product suite designed to meet the unique requirements of biopharmaceuticals management.

As a result, CLINapps will combine its complementary product offering with the Bracket clinical suite to deliver a wider range of digital solutions across a trial.

“CLINapps’ strong technology fits squarely into Bracket’s goal of transforming the way pharmaceutical companies manage data and interact with sites, investigators and patients,” said Jeff Knell, CEO of Bracket.

CLINapps’ product portfolio will be tightly integrated into Bracket’s eClinical product suite, which is expected to add significantly to the company’s existing randomization and trial supply management capabilities. In addition, SmartSupplies, CLINapps’ flagship enterprise clinical trial material management software solutions, will give Bracket the opportunity to manage end-to-end clinical inventory management for sponsors. Bracket’s new integrated solution will reportedly advance areas of demand planning (forecasting), inventory management, cold chain distribution and controls electronic batch records and overall quality control on the labeling, release, assignment and return of clinical trial materials.«
Focus shifts to new and developing tech not involving the direct use of animals
BY JENNIFER CLIFFORD
PRINCETON, N.J.—Since 1980, more than 30 drugs have been removed from the market due to concerns about hepatotoxicity and possible drug-induced liver injury (DILI) in patients. Several others have had their use restricted for the same reason. Currently, pharmaceutical companies spend valuable time and money on drug candidates only to have them withdrawn in late-stage clinical trials due to DILI.

In May 2015, a group was set up at Envigo to assess new and developing technologies that did not involve the direct use of animals, resulting in the Non-Animal Technology program, or NAT, which focuses on assessing new developments in in-vitro models and techniques and facilitating drug development. As part of this process, Envigo scientists investigated some of the major risks new drugs face during development and how they could use new in-vitro techniques to effectively gauge a drug’s susceptibility to various risks, including non-approval. Two aspects were chosen for further investigation: de-risking programs and an assessment of what assays are currently used to satisfy regulatory requirements and those tests currently being developed.

Recently, Envigo announced the launch of its new DILI assessment program, an integrated program of in-vitro technologies designed to help predict the likelihood of compounds causing DILI. The program is run by using either some or all of its three key tests as needed to identify whether a drug exhibits possible risk factors associated with drug-induced liver injury.

“Envigo’s battery of in-vitro tests, typically using human cells, enables our customers to determine if a compound carries a DILI liability. A compound that is negative in our in-vitro testing program is considerably de-risked from one of the failure factors newly approved drugs face. This allows our customers to make more informed choices as to whether they should progress the compound. The de-risking approach serves to increase patient safety, provides confidence to invest and aids the in/out-licensing of new drugs,” commented Gay Webber, scientific manager of the In Vitro and Drug–Drug Interaction Sciences Group at Envigo.

The tests used for the program—covalent binding, reactive metabolite formation and time-dependent inhibition (TDI) of cytochrome (CYP) enzymes—require mere milligrams of material. This makes them ideal for early discovery research, Envigo notes, where typically only small amounts of compound are available.

“If a compound comes up negative in these assays, we then use this data, in conjunction with other information, such as lipophilicity, transporter inhibition, structural alert analysis and likely human dose, to make an educated assessment as to whether a compound may carry a DILI liability or not,” Webber noted.

“Ultimately, the DILI assessment package forms part of Envigo’s larger de-risking program for new drugs. This broader initiative, driven by the company’s Science and Technology Advisory Group, comprises DILI assessment, drug–drug interactions, genotoxicity and cardiotoxicity,” added Brian Burlinson, principal scientist for safety assessment at Envigo. “As our de-risking studies can be carried out very early on, there is time for chemists to re-examine their molecules and assess potential changes that could be made to reduce the DILI liability while maintaining efficacy. Once the molecules are re-engineered, they can then be checked again against the Envigo assays.”

Currently, Envigo does not expect this program to affect how the FDA approaches new drugs or re-evaluate any that had previously been withdrawn or restricted, but added that information provided to customers will ultimately be of interest to the FDA, and that could potentially become a part of the approval process. The hope is that the highly focused and visible way Envigo provides customers with this type of information will help the agency judge both risks and benefits of new drugs efficiently, leading regulatory bodies to do the same.
INC
CONTINUED FROM PAGE 29
research sites worldwide, INC Research is inviting sites to join its Catalyst Community, an online forum designed to support ongoing communication and information exchange on the conduct of clinical trials, wider adoption of new methodologies and evolving best practices. The goal of the community, which is open to all clinical research sites, is to harness the input and insights from sites across the globe in order to develop best practices.

According to Tracey Gashi, executive director of site and patient access at INC Research, “The Catalyst Community is just one part of INC Research’s Catalyst program. The program builds on INC Research’s commitment to establishing longstanding and productive site relationships. Through the Catalyst program, INC Research aims to increase predictability and to drive new methodologies and continuous improvement in the delivery of clinical research.”

The other part of the Catalyst program is the Catalyst Site Network. “The Catalyst Site Network consists of a select set of high-performing sites that are strategically aligned to INC Research’s business and that of our customers,” Gashi explains. “These networks are therapeutically aligned and consist of a variety of sites, including individual practices, academic centers of excellence and site networks. INC Research works with these sites to gather input and insights from our global clinical research sites when developing best practices for clinical research.”

The two halves are very much meant to complement each other. “The Catalyst Community is an online forum which is open to all sites, and it provides INC Research with the opportunity to engage with a broader group of sites to support ongoing communication on the conduct of clinical trials, wider adoption of new methodologies and best practice sharing. It also enables sites to have a voice into the initiatives borne out of the Catalyst Site Network,” says Gashi. “The forum accessed through the incConnect for Investigative site platform also gives all sites access to many of the benefits the Catalyst Sites receive in a self-service format.”

While at the SCRS summit, INC Research also presented new insights from a paper titled “Addressing Pain Points of Investigator Payments for Clinical Trials.” This paper addresses the challenges surrounding site payments, and highlights key insights from the INC Research Site Advocacy Group (SAG), which was established to address such issues and outline initiatives to improve the process.

“Issues regarding payment to sites for services conducted on clinical trials has been a longstanding issue, and one that INC Research has been keen to understand and respond to,” says Gashi. “In order to achieve this, INC Research was the first CRO to engage with sites through SAG, in collaboration with SCRS. As a result of the feedback gathered from the sites as part of the SAG, INC Research has already streamlined our internal processes to address a number of these issues, and has published a white paper summarizing the challenges sites face surrounding site payments and the initiatives already underway to improve this process.”

INC Research has served as a member of SCRS, as well as a Global Impact Partner to the organization, since 2014. By partnering with SCRS, INC Research says it is contributing to making clinical research more sustainable for clinical research sites, and the company points out that through it sponsorship activities with SCRS, INC has funded more than 500 site scholarships that provide the training, mentorship and advocacy that sites need to become members of a world-class clinical research community. INC Research is also actively engaging with the SCRS to strengthen and grow its global membership through the SCRS Ambassador Program.

“INC Research is also committed to building awareness of, and participation in, clinical trials. By bringing together the research enterprise in novel ways and driving the conversation around barriers and motivators for patients, INC Research aims to increase clinical trial participation,” Gashi tells DDNews. “The ‘Inspiring Hope’ Ideathon held in September 2016 by INC Research and CISCPR continues to raise awareness and understanding of clinical trials while supporting health literacy with patients, healthcare professionals and the general population.”

For more information, visit www.DDN-News.com
Horizon announces bioproduction outlicense deal with unnamed partner

By Ileene Schneider

Cambridge, U.K. – In October, Horizon Discovery Group plc, which specializes in the application of gene-editing technologies, announced a new licensing agreement with an unnamed commercial partner for access to Horizon bioproduction cell lines.

The subscription deal, which is valued at a minimum of £500,000, is a novel licensing model that enables early access over a five-year period to bioproduction cell line innovations and immediate use of Horizon’s GS Null CHO K1 bioproduction cell line for drug manufacturing. The collaboration will allow the partner to license, via the subscription, any follow-on cell lines developed as part of the program at a 50-percent discount within a five-year period. The minimum fee will be paid up front, with a significant amount to be recognized in fiscal year 2016.

The license deal follows an evaluation period initiated in the fourth quarter of 2015. It HORIZON CONTINUED ON PAGE 33

Commenting on Cures

By Jeffrey Bouley

Having shared my feeling about the 21st Century Cures effort in the U.S. Congress (see my editorial on page 10 of this issue), I thought I’d share the several comments from other organizations that have passed through my email inbox.

The latest version of the bill easily made its way through the House of Representatives and, as of the final production of this issue (and after the comments below were made) had just passed the Senate.

Avalere Health

Just prior to the passage of the Cures bill in the House, strategic advisory company Avalere Health had some thoughts. Breaking down the legislation, Avalere noted that key provision changes include the following:

• Increased funding levels for both the FDA and the NIH have been trimmed since earlier versions. New funding for the FDA is now at $500 million (previously $550 million) and NIH is now at $4.8 billion (previously $9.3 billion). Despite these reductions, funding for precision medicine and the BRAIN initiative remain in place.

• Provisions in this bill are now organized into more therapeutic areas, as well as class-

BRIEFS

Boehringer Ingelheim sets aside omultinib program

ROSEFIELD, Conn.—In the wake of reevaluating the clinical data on omultinib, a third-generation EGFR-targeted therapy, Boehringer Ingelheim will be returning the drug candidate’s development and global commercialization rights to Hami Pharmaceutical Co. Ltd. Boehringer Ingelheim will not be launching new clinical trials for omultinib, but will work with Hami Pharmaceutical to transition the current clinical development program back to the latter company.

“We would like to thank Hami Pharmacetical for their collaboration and commitment during our joint development of omultinib. Partnering is a key pillar of our oncology strategy at all stages of research and development, in order to offer cancer treatments that fit the needs of patients, caregivers and healthcare professionals. Boehringer Ingelheim’s oncology pipeline is robust and transformative, and we strive for best-in-class, breakthrough cancer medications,” Dr. Jörg Barth, corporate senior vice president, therapeutic area head oncology, Boehringer Ingelheim, said of the decision.

Demiria, Maruho ink license deal

MENLO PARK, Calif.—Biopharmaceutical company Demiria Inc. and Maruho Co. Ltd. have struck up an exclusive license agreement under which Demiria has granted Maruho an exclusive license for the development and commercialization of DRM04 in Japan. The product candidate is a topical anticholinergic being developed for the treatment of primary axillary hyperhidrosis (excessive underarm sweating). Per the terms of the agreement, Maruho will fund all milestones and sales thresholds are met, as well as make an initial license payment to Demiria of $25 million. Demiria also stands to receive additional payments totaling up to $70 million if certain milestones and sales thresholds are met, as well as royalties of up to a low double-digit percentage of net product sales in Japan. Maruho will fund all development and commercial costs for DRM04 in Japan and, pending talks with Japanese authorities, intends to launch a Phase 1 clinical trial for DRM04 in Japan.

Horizon Discovery recently secured a new licensing agreement with an unnamed commercial partner for access to Horizon bioproduction cell lines.

Galvan on the cutting edge

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

By Jeffrey Bouley

LONDON—Heading up this month’s tour through recent news of life-sciences tools of the trade, we have news from Puridify Ltd., developers of novel bioprocessing purification technologies for industrial biomolecule manufacture, that they have signed an 18-month collaboration deal with GlaxoSmithKline to extend the evaluation of Puridify’s FibroSelect purification technology with a view to building a package to support potential use of nanofibers in toxicology and clinical manufacture.

This signing follows a previous 18-month collaboration which reportedly has seen successful demonstration of proof-of-concept studies at the 50-liter scale, with potential calculated economic benefits based on the technology’s use.

Venture-backed Puridify says it has been on a rapid path of development and commercialization to deliver an industry-ready technology that will allow a step-change in current downstream processing of industrial bio-therapeutic manufacture. The unique high capacity combined with high
Improving FDA metrics and ‘quality culture’

CPhI Worldwide experts propose new FDA quality metrics system and recommend critical formulation attributes

by DDNEWS STAFF

AMSTERDAM, The Netherlands—This fall, CPhI Worldwide, organized by UBM EMEA, announced that one of part one of the “2016 CPhI Annual Report” on potential new approaches to improve quality and manufacturing process in pharmaceutical production ahead of CPhI Worldwide 2016 in Barcelona, Spain. As CPhI noted, five world-renowned experts—Aajus Hussain, Girish Malhotra, Brian Carlin, Pabir Basu and Thomas Friedli—propose improved methods to how we evaluate formulations in the pharmaceutical industry, making a number of key recommendations.

According to CPhI, the overall findings reveal there are a number of improvements industry and the regulators can and should make to shift the industry from just meeting standards towards instilling continuous improvement and quality cultures across the board, which the panel predicted will vastly improve overall quality and reduce manufacturing errors.

Independent consultant Basu and Friedli, a professor at the University of St. Gallen, reviewed a new systems-based approach to quality metrics in their article, following the university receiving a U.S. Food and Drug Administration (FDA) grant to undertake the effort. He added: “Continuous monitoring of impact from all excipients throughout the lifecycle is more important than a one-off arbitrary binary classification during development. The importance of all attributes and parameters should be evaluated for impact, and re-evaluated as new information becomes available.”

Emphasizing the panel’s concern regarding the need to shift towards quality cultures and away from binary measures of product failure, Hussain, who is CEO at Insight Advice & Solutions LLC, stated that the “file first, figure it out later” mindset is a fundamental part of the problem. He believes that companies that implement quality by design (also referred to as QbD) and process analytical technology (PAT) approaches early in development will see the greatest benefits and have the capabilities to file first, adding, “Broader adoption of PAT-based continuous manufacturing system by brand and by a couple of major generic and CDMOs should be more prominently evident in the next three years.”

Carlin believes the industry is now at a “tippping point” with the first adopters of continuous processing having been included in NDAs, and an excellent opportunity now exists for the manufacture of injectables and vaccines to make more progress over the next three years. However, he argued the ability to manufacture continuous, while significant, is, in fact, a business decision.

Malhotra, who is president at EPCOT International, suggests that while there is much excitement around continuous processing, we must better define what it is we mean by “continuous” given that in terms of active pharmaceutical ingredients (APIs), very few products have the scale to be manufactured truly continuously. There simply aren’t the volumes needed, and the industry’s greatest shortcoming is its overall record of manufacturing technology innovation. As he noted, “All said and done, each company producing APIs or their formulations has to justify and use the most cost-efficient technology (batch, campaign batch or continuous) to produce products that are economic and deliver the same quality all the time. Regulators can only regulate and assure product quality. They can suggest the technologies and methods companies should consider for their products. However, companies have to justify use of such technologies."

“[O]ur experts believe that continuous improvement programs and ongoing analysis are more important to instilling a quality culture than simply striving to achieve minimum regulatory standards.”

Chris Kilbee of CPhI should see a shift towards harmonized standards and more advance manufacturing. By implementing the recommendations from our panel, the pharma industry will advance more quickly, develop better and safer drugs and realize the full potential of lower cost and higher-quality manufacturing.”

CPhI’s goal is to drive growth and innovation at every step of the global pharmaceutical supply chain, from drug discovery to finished dosage. Through exhibitions, conferences and online communities, CPhI brings together more than 100,000 pharmaceutical professionals each year to network, identify business opportunities and expand the global market. CPhI hosts events in Europe, Korea, China, India, Japan, Southeast Asia, Istanbul and Russia.

Horizon

CONTINUED FROM PAGE 32

reflects the partner’s confidence that Horizon will provide a number of additional cell lines over the next five years, leading to significant efficiency improvements in its biomanufacturing capability, according to the company.

“Horizon continues to be a disruptive influence in the bioproduction arena, using technical and commercial innovation to accelerate advancements in drug manufacturing,” said Dr. Darrin Disley, CEO of Horizon Discovery Group. “This new announcement further validates our approach, with our partner demonstrating confidence by making a five-year commitment via subscription model to the program. We look forward to making further announcements in this area as Horizon continues its momentum as a key player in the bioproduction space.”

In November, Horizon Discovery said that its continued collaboration with CareDx Inc. was another deal that clearly validates its model. Disley explained that Horizon makes cell lines that can be used to stand in for real patient samples, and firms developing assays and research tools can utilize them. The agreement is to supply what Horizon calls “cell-free DNA-based molecular reference standards” to CareDx as part of the latter’s research into transplanted organ rejection.

“Horizon continues to be a disruptive influence in the bioproduction arena, using technical and commercial innovation to accelerate advancements in drug manufacturing,” says Dr. Darrin Disley, CEO of Horizon Discovery Group. “This new announcement further validates our approach, with our partner demonstrating confidence by making a five-year commitment via subscription model to the program.”

“It’s an important area as often patients’ own samples are not available or consistent enough for reliable usage,” explained Chris Claxton, the firm’s vice-president for investor relations and corporate relations. “It provides an initial revenue stream to start with and the potential that groups like CareDx will continue to use them as a partner longer term. We are looking to do many CareDxs. We’re looking to layer on many, many revenue streams, not just from a single organization.”

Protein therapeutics represent a significant share of the top 50 drugs globally and are increasingly present in developmental pipelines. The provision and licensing of bioproduction cells for their manufacture, however, can be cost-prohibitive, especially for smaller organizations, and are often tied to long-term revenue-based licensing terms.

Horizon was founded by Dr. Chris Torrance and Prof. Alberto Bardelli in 2007 when they came across a seminal discovery by Prof. David Russell that certain forms of aden-associated virus (AAV) were more than 1,000 times more efficient at gene targeting in human somatic cell types than plasmid-based methods. Horizon design engineers genetically modified cells and uses them in research and clinical applications to advance human health worldwide. Its core capabilities are built around its proprietary transnational genomics platform, a suite of gene-editing tools such as AAV, ZFN and CRISPR to alter almost any gene sequence in human or mammalian cell lines."

Exclusive web content: New Q&A online

Recently, Robert Jacks, president and chief financial officer of SymbioMx, discussed briefly with DDNews the company’s product Solosec (secnidazole), a next-generation 5-nitrimidazole antibiotic. To read this Q&A, you can go to our website at www.ddn-news.com and do a search for its Editconnect number: E121632.
ROCKVILLE, Md.— OriGene Technologies, manufacturers are already proving the benefit of single-use purification units will enable this packed and ready to operate, "commented focused on generating industry-relevant end–when cycled over 190 times with three–of operation, FibroSelect units have dem–improve process robustness and increase to-operate units reduce validation burden, are more than 50 times larger. The ready–to enable the replacement of columns that flowrate properties of FibroSelect are said adaptation of KO validation in the antibody tific officer and founder of EdiGene: "The such as CRISPR. "

Cell Lysates and use of leading technologies research through the delivery of Knockout products. Through our unique relationship in genome-editing technology and OriGene's genome-wide knockout cells from commonly entered into a multiyear strategic agreement eight, however, to move from on-premise to the new hosted Enterprise Reagent Manager. ERM replaces four legacy chemical inventory management solutions at their four different sites in the United States and Europe, providing–antibody performance is verified and target existing database's powerful search options to sell and support the integrated systems to the medtech, medical device and diagnostics industries. "The combination of FocalSpec's optical measurement technology with Ginolis' automation platform allows Ginolis to sell and support the integrated systems to the medtech, medical device and diagnostics industries."

The introduction of novel tools such as the ready-made Knockout Cell Lysates has the potential and currently lacking. The Knockout Cell Lysates from OriGene are specifically designed to drastically improve the process by which antibody performance is verified and target specificity is confirmed by scientists. "The introduction of novel tools such as the ready-made Knockout Cell Lysates has the potential and currently lacking. The Knockout Cell Lysates from OriGene are specifically designed to drastically improve the process by which antibody performance is verified and target specificity is confirmed by scientists."

R packages that drive efficiency by putting the patient in the center of the healthcare prod–uct commercialization process." Agilent launches new panel for fast FISH testing

RESEARCH TRIANGLE PARK, N.C.—Sci–Quest, a leading provider of spend manage–ment solutions, announced recently that a leading global pharmaceutical company has implemented SciQuest's Enterprise Reagent Manager (ERM) to enhance inventory man–agement, shopping and compliance within their research and development facilities. Eight of the 10 top global pharma–ceutical companies, ERM allows scientific staff to find, source and track mission-critical materials from a single application. This par–ticular top pharma client is the first of those eight, however, to move from on-premise to the new hosted Enterprise Reagent Manager. ERM replaces four legacy chemical inventory management solutions at their four different sites in the United States and Europe, providing–antibody performance is verified and target existing database's powerful search options to sell and support the integrated systems to the medtech, medical device and diagnostics industries. "The combination of FocalSpec's optical measurement technology with Ginolis' automation platform allows Ginolis to sell and support the integrated systems to the medtech, medical device and diagnostics industries."

The tests in vaccination show the ability to rapidly review and select the most appropriate model for their in-vitro studies.

"We’ve come a long way since the release of our first version of XenomeBase," said Dr. Qian Shi, vice president of cancer pharmaco–logy and in-vitro cancer biology at Crown Bio. "Getting instant access to in-vitro pharma–cology data linked to in-vivo data from the corresponding cell line-derived xenograft in one comprehensive and easy-to-browse plat–form means clients will be able to plan their studies with an end-to-end solution in mind."

"I think it’s already taking advantage of the new feature, while new clients can simply send a request to register to start using the service from the company website.

Fluidigm introduces high-parameter panels for immune-oncology research

SANTA CLARA, Calif.—This fall saw Fluidigm Corp. introduce a modular set of high-parameter Maxpar mass cytometry panels for immune-oncology research. Designed for use with Helios and CyTOF systems, the new ImmunoXenome Panels will make it easier for researchers to seamlessly integrate their own antibodies into the Fluidigm platform. "The new ImmunoXenome Panels will make it easier for researchers to seamlessly integrate their own antibodies into the Fluidigm platform."

The new panel, comprising of ALK, ROS1, RET and MET IQUEST probes, was designed using the oligonucleotide-based SureFISH technology utilizing formamide-free IQUEST fast hybridization buffer.

"We are excited about the upcoming probe launches for Dako Omnis," said Jacob Thaysen, president of Agilent's XenoBase, and Genomics Group. "Agilent is committed to–groundbreaking research in the field of immuno-oncology. "

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CURES
CONTINUED FROM PAGE 32

allocated to the ACA’s Prevention and Public Health Fund and territory funding. Other offsets include Medicare and Medicaid payment changes.

“Cures has generally had broad bipartisan support because many of its provisions are intended to help get medical products to patients faster without sacrificing FDA’s central safety and effectiveness mandate,” said Jay Jackson, manager at Avalere Health. “Provisions that were debated and not included in the current iteration of the bill, such as FDA guidance on off-label communication and laboratory-developed test regulation, may well reappear through further amendments, the upcoming user fee re-authorization and other regulatory or legislative actions.”

Kids v Cancer
Nancy Goodman, executive director of Kids v Cancer, was among those giving a thumbs-up to the passage of 21st Century Cures in the House and urging Senate approval as well. Of note to her was that the legislation includes wording on the Creating Hope Act Pediatric Priority Review Voucher Program. Specifically, pursuant to 21st Century Cures, the Creating Hope Act Pediatric PRV program will be extended to Sept. 20, 2020. Moreover, rare pediatric disease drugs that receive designations by that date will have until Sept. 20, 2023 to earn a voucher.

“This is a landmark step for our kids,” said Goodman. “Going forward, drug companies will continue to have an opportunity to develop drugs for children with cancer and other life-threatening illnesses. The Creating Hope Act works. It has generated almost $1 billion in industry-funded incentives already.”

Biotechnology Innovation Organization
The Washington, D.C.-based Biotechnology Innovation Organization (BIO) was also praising the progress of the bill. President and CEO James C. Greenwood noted, “The 21st Century Cures Act passed by the House of Representatives today is an important victory for patients and for the next generation of medical innovation. The legislation advances important patient-centered policies that can speed the pace of drug development, while authorizing essential funding for scientific discovery and the promotion of biomedical advancements that can help transform healthcare for patients with the promise of next generation modern medicines.”

American Society of Clinical Oncology
In a statement about 21st Century Cures, Dr. Daniel F. Hayes—president of the American Society of Clinical Oncology (ASCO)—wrote: “Today, by passing the 21st Century Cures Act, the U.S. House of Representatives took a significant step forward to accelerate the pace of bringing promising new treatments to patients, including the 1.6 million Americans diagnosed with cancer each year... The 21st Century Cures Act will provide a much-needed boost in supplemental funding to the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) to support critical cancer research and accelerate the momentum of the Cancer Moonshot Initiative. The $4.8 billion for NIH and $500 million for FDA will help spur advances in cancer prevention, detection, diagnosis, treatment and quality of life of patients.”

ASCO is also particularly pleased that the bill takes a step forward in addressing the interoperability of electronic health records and that the legislation puts restrictions on intentional information blocking.

“These much-needed improvements will make it easier to coordinate patient care across a variety of medical providers—and advance important efforts on Big Data and precision medicine. Big Data initiatives, such as ASCO’s own CancerLinQ, rely on the ability to share massive amounts of clinical data from large groups of cancer patients,” according to Hayes.

Public Citizen
Advocacy group Public Citizen has pretty much been against 21st Century Cures from the start, and its view was expressed the day of the House vote by Dr. Michael Carome, the group’s director of health research, as: “The U.S. House of Representatives, after weeks of secret deliberations, today passed the dangerous 21st Century Cures Act. The bill has been sold erroneously as a commonsense, bipartisan compromise that enables scientific innovation and medical breakthroughs for America. But in reality, the legislation includes a grab bag of goodies for Big Pharma and medical device companies that would undermine requirements for ensuring safe and effective drugs and medical devices.

“Moreover, many House members were persuaded to support the bill, despite the many harmful provisions, in exchange for promises of increased funding for the National Institutes of Health. But there is no guarantee that this funding will be appropriated by Congress in future years. Permanently weakening the U.S. Food and Drug Administration in exchange for tens of billions of increased NIH funding is a bad deal for patients.”

For more information, visit www.DDN-News.com
Robert Speth receives Provost’s Research and Scholarship Award

FORT LAUDERDALE, Fla.—In recognition of his significant contributions to Nova Southeastern University (NSU), Dr. Robert C. Speth recently was named the recipient of the Sixth Annual Provost’s Research and Scholarship Award. Speth, a researcher and professor of pharmaceutical sciences in NSU’s College of Pharmacy, was presented to Frey at the AAALAC International Global 3Rs Award for multi-tissue experiments and call “body on a chip” systems. Such systems serve as complex microfluidic channels to mimic the cardiovascular system. In the course of his career, he has secured more than $1 million in funding for his research through 22 externally funded projects. Also, he has served or is currently serving on the editorial boards of such journals as Regulatory Peptides, the Journal of Pharmacology & Clinical Toxicology and the International Journal of Peptides. He has served as an ad-hoc reviewer for 39 journals, including Science.

“Dr. Speth has distinguished himself as a researcher, an educator and a staunch supporter of the NSU community,” said Dr. Ralph V. Rogers Jr., NSU executive vice president and provost. “He has truly demonstrated what this award is meant to recognize: innovative and sustained activities in support of NSU’s mission to foster intellectual inquiry, academic excellence, research and a dynamic learning environment.”

“This is the greatest honor that has ever bestowed upon me,” said Speth of the award. “What makes it even greater is the fact that there are so many other incredibly talented faculty members in the NSU family who are also deserving of this recognition. I dedicate this award to my mentor Hank Yamamura, who taught me to always make the best interests of my students my highest priority, and it is those very same students who paved the way for me to receive this honor.”

France Biotech grants ‘Entrepreneur’ awards

PARIS—In late November, France Biotech, an organization representing French entrepreneurs in life sciences and their business partners, awarded the winners of its 2016 Entrepreneurs in Health awards, which are aimed at recognizing entrepreneurs who are managing companies in the health industry and have achieved significant breakthroughs in their clinical and financial development in 2016. The “Woman Entrepreneur in Health” award went to Cécile Réal, co-founder and chairman of Endo-diag, a biotechnology company specialized in the development of endometriosis diagnostic solutions. The company has developed blood diagnostic, prognostic and predictive tests currently conducting validation studies that have the potential to dramatically reduce diagnosis delays.

Hervé Affagard was recognized as “Man Entrepreneur in Health.” He is the CEO of Maat Pharma, a company located in the Lyon region and specialized in the gut microbiome. The company entered in clinical development to continue the development of its first medicinal product for the treatment of dysbiosis (gut microbiome imbalances) following the treatment of diseases such as large-scale antibiotic therapy or chemotherapy. The company raised €10 million in March 2016, totaling €15 million funded within 18 months. As a global pioneer in antologous fecal microbiota transfer, Maat Pharma inaugurated early November the first European proprietary platform dedicated to this problem, carrying its trial into the field of hematology-oncology.

Also, Bernard Gilly received the 2016 “Coup de Cœur Entrepre- neur in Health” award. He is the co-founder and CEO of Genisight Biologies, a company specializing in the development of novel therapies for mitochondrial and neurodegenerative diseases of the eye and central nervous system that leverage enzymes. Inovio became the first listed gene therapy company in Europe while raising €45.2 million. Topline results of INOVIO are set to be announced in the coming months.

Once again this year, the France Biotech entrepreneur awards are honoring exceptional men and women whose stamina, mobilization and will to change the world drive major scientific breakthroughs,” said Maryvonne Hiance, chairman of France Bio-tech. “Cécile Réal, Hervé Affagard and Bernard Gilly are outstanding representatives of the French Entrepreneurship, an attitude and a philosophy of life that we have been cherishing and defending for many years. These awards are a testament of our gratitude and admiration.”

InSphero scientist recognized for body-on-a-chip system

SCHLIEREN, Switzerland—In early November, Dr. Oliver Frey of InSphero AG received the 2016 IQ Consortium and AAALAC International Global 3Rs Award for Europe, recognizing his pioneering work to integrate advanced 3D microtissue models called “body on a chip.” Such systems are designed to develop a scalable, flexible technology.

Inovio wins Deloitte’s Fast 500 award

PLYMOUTH MEETING, Pa.—Inovio Pharmaceuticals Inc. recently announced it ranked at 107 on Deloitte’s Technology Fast 500, a ranking of the 500 fastest-growing technology, media, telecommunications, life-sciences and energy tech companies in North America. Technology Fast 500 award winners are selected based on percentage fiscal year revenue growth from 2012 to 2015. During this period, Inovio’s revenue growth reached 885.1 percent, based on revenue received from grants, partnerships and licensing deals.

Also, in October, the company noted that its president and CEO, Dr. J. Joseph Kim, was selected as a 2016 Healthcare Innovator by a panel of scientific and medical experts convened by the Philadelphia Business Journal. The annual award honors the people and companies who are disrupting the healthcare and biotechnology industries and solidifying Greater Philadelphia’s reputation as a center for innovation.

Kim is a pioneer of DNA-based immunotherapies and vaccines which are designed to attack and prevent cancers and challenging infectious diseases. Inovio has an extensive pipeline of clinical-stage cancer immunotherapies highlighted by VGX-300, which is entering Phase 3 trials this year for a cervical preancer, as well as DNA vaccines in development infectious diseases for Zika, MERS and HIV, among others.

SAFE-BioPharma partnership named HHS winner

WASHINGTON, D.C.—The Office of the National Coordinator for Health Information Technology of the U.S. Department of Health and Human Services (HHS) named a proposal from SAFE-BioPharma, Resilient Network Systems and WebShield Inc. as a phase one winner of the Move Health Data Forward Challenge. The competition identifies ways to enable consumers to share their personal health information safely and securely with their healthcare providers, family members or other caregivers. Here at DDNews, we think such advancements may be useful to clinical trials and post-market drug studies as well.

SAFE-BioPharma partnered with Resilient Network Systems, WebShield, Carebox and InterSystems to create a solution that gives consumers the ability to conveniently access and share their health data on demand. The solution will demonstrate a unique nationwide capability to conveniently verify a consumer’s identity, locate and electronically request a consumer’s records, and deliver them to a secure cloud-based personal storage service.

HHS selected 10 phase one winners, which will be narrowed to five finalists and then to two winners.
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The system is:
- **Fast** – Accurate results in less than a minute right at your bench
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- **Powerful** – Bead- and cell-based experiments at the push of a button

Cell Signaling Technology Inc.
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**Molecular identifiers improve detection of low-frequency mutations**

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Swift Biosciences have introduced Molecular Ids (MIDs) for NGS library prep to maximize your ability to confidently detect low-frequency mutations by removing false positives generated in your sequencing data. Increase the sensitivity of your exome and small-panel sequencing data with MIDs. Download our guide to get the most out of your cDNA and FFPE samples.

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Introducing the New ZE5 Cell Analyzer with all of the features you’ve been asking for in your next flow cytometer:  
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**New Zika virus reference materials**

**ATCC**

ATCC has expanded its collection of Zika virus reference materials to include new isolates from Puerto Rico (ATCC VR-1843), Columbia (ATCC VR-1844) and Huarazas (ATCC VR-1848). Growth of these strains is supported by ATCC’s broad range of cell lines and associated reagents, including a new line of human neural progenitor cells for in-vitro pathogen-host interaction studies.

ATCC
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Promega’s Characterize your immune-modulating antibodies the best way possible. Our reporter bioassay platform uses standardized controls and reagents plus cells in a three-and-use format that eliminates the uncertainty of using primary cells. Use the PD-1/PD-L1 Immune Checkpoint Bioassay to measure the potency and stability of antibody candidates designed to block the PD-1/PD-L1 interaction and to measure antibody function throughout drug research and development.

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**Affordable benchtop 1536-well pipetting**

**INTEGRA Biosciences AG**

INTEGRA has introduced a new plate holder enabling 1536-well pipetting on its VIAFLO 384 electronic handheld pipette. This introduction provides screening labs with a unique alternative to the complexity and cost of fully automated robotic liquid handling systems. The VIAFLO 384 is the only benchtop pipette on the market which allows easy and precise pipetting into 1536-well plates. To watch a video on 1536-well pipetting on the VIAFLO 384 visit the company website.

INTEGRA Biosciences AG
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**Trypsin/Lys-C Mix: See what you’ve been missing**

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Trypsin/Lys-C Mix, Mass Spec Grade, improves protein digestions using the standard digest protocol by eliminating the majority of missed cleavages, which occur frequently in standard trypsin digests. Trypsin/Lys-C Mix improves reproducibility of digest results and the ability to generate data from poor quality sample materials, such as those containing contaminants and trypsin-inhibiting compounds.

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**Streamline CRISPR gene editing**

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**Affordable ddPCR assays instantly with new website**

**Bio-Rad Laboratories Inc.**

Bio-Rad’s new Droplet Digital PCR (ddPCR) Assay Design Website takes the guesswork out of ddPCR assay design and allows users to instantly design mutation detection or copy number assays for any target. Well lab validated assays guaranteed to work can also be found on the site as well as thousands of predesigned assays, which were created using the same design criteria to deliver reliable and robust ddPCR results.

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**Bio-Rad Laboratories, Inc.**

For more information, visit www.DDN-News.com
Newcomer Axial looks to harness gut microbiome to treat CNS disorders

BOSTON—With the end of November came the launch of Axial Biotherapeutics, which announced a $19.15-million Series A round of financing as part of its introduction to the central nervous system (CNS) and gut microbiome therapeutic spaces.

The company seeks to leverage what it calls the “groundbreaking work” of co-founder Dr. Sarkis Mazmanian, which uses the gut microbiome to help treat CNS-related diseases and disorders.

“By interrogating the biological link between the gut microbiome and the brain, we are discovering pathways and mechanisms that can be leveraged to develop novel treatment options for vastly underserved diseases,” said Mazmanian. “The discovery that changes in the gut microbiome may cause neurological diseases is a paradigm shift and opens entirely new possibilities for treating patients. I am looking forward to working with the team at Axial to translate our breakthrough discoveries in the laboratory to patients in need.”

Mazmanian is the Louis & Nelly Soux Professor of Microbiology in the Division of Biology and Biological Engineering at the California Institute of Technology (Caltech). The Mazmanian Laboratory was among the first to demonstrate disease-modifying effects in mouse models of autism spectrum disorders (ASD) via novel and proprietary microbiome interventions. Axial will leverage those findings to build a microbiome discovery platform targeting the gut-brain axis which provides the opportunity to generate a diverse pipeline of new therapies for patients with neurological diseases and disorders.

Axial has licensed exclusive, worldwide rights to intellectual property which covers a novel and proprietary class of CNS biotherapeutics from the Mazmanian Laboratory at Caltech. Axial’s focus will be to translate these discoveries into a unique class of microbial-targeted biotherapeutics that could become breakthrough therapies for a variety of neurological diseases and disorders, including ASD and Parkinson’s disease.

In conjunction with the financing, Axial Biotherapeutics announced the appointment of company co-founder Dr. David H. Donabedian as CEO and board director. Additional Axial board members include Dr. James C. Blair, a partner at Domain Associates; Dr. Michelle Dipp, a partner at Longwood Fund; and Caltech’s Mazmanian.

The Series A financing was led by Longwood Fund and Domain Associates. Also participating in the financing were Karios Ventures, Heritage Medical Systems and a group of high-net-worth individuals based in Southern California.

“I look forward to developing this world-class science into treatments which have the potential to help patients where limited treatment options are available,” said Donabedian. “There is mounting evidence that the gut microbiome is implicated in brain development and neurological health, and we believe we are at the forefront of generating new avenues for microbiome-targeted therapeutic interventions in multiple neurological diseases and disorders.”

AdAlta licenses Alzheimer’s-specific shark antibodies to Crossbeta

MELBOURNE, Australia & UTRECHT, Netherlands—AdAlta Ltd., a biotechnology company specializing in the discovery and development of protein-based therapeutics, and Crossbeta Biosciences, a biotechnology company with unique technology for therapeutic and diagnostic use in neurodegenerative disorders, in November announced a commercialization agreement under which Crossbeta has been granted an exclusive license to three beta-amyloid oligomer (AβO)-specific shark antibodies, identified under the collaboration signed between AdAlta and Crossbeta in December 2015.

These shark antibodies are considered to have immediate and highly disease-specific potential for the diagnosis and treatment of Alzheimer’s disease. Combining the unique strengths of both companies, the research and development collaboration used AβOs produced by Crossbeta’s proprietary oligomer-stabilizing technology and then employed AdAlta’s single-domain shark antibody library to screen these novel targets to identify the therapeutic and diagnostic lead candidates.

The three licensed anti-AβO antibodies bind specifically to the disease-relevant AβO preparation but, importantly, do not recognize or bind to the monomer and fibrils of the beta-amyloid protein, the companies say. AdAlta will receive royalties on future revenues from successful commercialization of the AβO-specific shark antibodies as novel therapeutics or diagnostic agents. All ongoing R&D as well as commercialization will be managed by Crossbeta.

“Crossbeta’s novel and unique oligomer-stabilization technology enabled us to identify Alzheimer’s disease-specific shark single domain antibodies with highly valuable differential binding properties. The long loop of the shark single-domain antibody (or i-body) binds to unusual epitopes with high affinity and specificity, as demonstrated with our lead candidate to a GPCR and previous targets and, most recently, in this instance with Crossbeta’s AβOs,” said AdAlta CEO Samantha Cobb. “This licensing deal fits with our strategy to focus on the i-body platform and our lead candidate in fibrosis, and we believe that Crossbeta with its strong position in the therapeutic area of Alzheimer’s is the right partner to realize the potential of these novel antibodies.”

Added Crossbeta CEO Guus Scheefhals: “We are very pleased with the outcome of our collaborative agreement with AdAlta, exploiting the promising characteristics of our AβOs to the future benefit of the Alzheimer’s field and patients. We will now move forward with developing these novel anti-AβO antibodies as potential treatments of real disease-modification potential and diagnostic use, as early in the disease as possible, for the benefit of Alzheimer’s patients.”

“Samantha Cobb, CEO of AdAlta

“The long loop of the shark single-domain antibody (or i-body) binds to unusual epitopes with high affinity and specificity.”

Samantha Cobb, CEO of AdAlta
“Finding bacterial molecules in the brain was a surprise, and finding more in the Alzheimer’s brains was a great surprise.”

Frank Sharp of UC Davis

UC Davis researchers have found higher levels of gram-negative bacteria in the brains of Alzheimer’s disease patients, but now must determine if the pathogens are causative or perhaps a result of Alzheimer’s. Pictured here is the Sacramento campus of the UC Davis Health System.

UC Davis researchers have found higher levels of gram-negative bacteria in the brains of Alzheimer’s disease patients, but now must determine if the pathogens are causative or perhaps a result of Alzheimer’s. Pictured here is the Sacramento campus of the UC Davis Health System.

Fourteen of 18 Alzheimer's brains were found to have higher levels of gram-negative bacteria. These findings, the researchers say, highlight the need to further investigate how infectious agents impact Alzheimer’s. While discovering LPS and K99 in Alzheimer’s disease brain samples is a good start, researchers must study the role bacteria may play in the disease pathology. A proven link between bacterial infections and Alzheimer’s could offer new opportunities to prevent and treat the disease.

“LPS is causative, we could immunize against LPS or treat gram-negative infections more vigorously than we normally do,” Sharp said.

The results will need to be replicated in larger studies to be confirmed.

“We detected these bacterial components in aging brains,” said Zhao. “Our next step will be to work out if this is the cause or the consequence of Alzheimer’s disease. Do gram-negative molecules cause the disease, or is it that when people get Alzheimer’s more bacterial molecules get into the brain?”

TUM eyes immunoproteasome inhibitors to tackle autoimmune disease

MUNICH, Germany—The immunoproteasome system to recognize abnormal cells. However, and in chronic inflammations and autoimmune diseases this “information channel” is overactive. Now researchers at the Technical University of Munich (TUM) have determined the molecular mechanisms of inhibitors that can selectively thwart the human immunoproteasome, which they see as important insights for the targeted development of new drugs.

As TUM notes of the research work, our immune system protects us from harmful infection, however, to recognize that something has gone awry in an afflicted cell, information on the proteins currently present inside the cell is required. This important task is handled by the immunoproteasome, a large, cyto- dromal protein complex that decomposes proteins and ensures that the fragments potentially address devastating genetic disorders. "With this expertise in the manufacture of lentivirus, and proven experience of working with global pharma companies, " said Huber.

“Knowledge about how various inhibitors target both proteasome types will therefore be leading the global clinical development and commercialization of collaboration programs in Europe, the United States and in other regions.”

Monalizumab progresses in trial as single agent in cancer treatment

MUNICH, Germany—The immunoproteasome is the proteasome, which has a different task from the immunoproteasome—blocks solely the immunoproteasome. But it is scientists trying to develop drugs that inhibit the immunoproteasome to prevent the mistaken attack healthy tissue, to undesired inflammation reactions. "In the past, we knew that certain agents attack immunoproteasomes stronger than constitutive proteasomes, but we did not understand why," explains Gross. "Knowledge about how various inhibitors target both proteasome types will therefore facilitate the development of compounds with higher selectivity and efficacy."

The researchers were also able to reveal the reason why many inhibitors bind much better to human immunoproteasomes than to the immunoproteasome of mice: “A single amino acid, in which the test compound is inserted, causes the active agent to ‘jam’ in mice, while it can easily dock to the human protein complex. This is important for the pharmaceutical industry, because it suggests that certain inhibitors should not be tested on mice," says Huber.

An inhibitor whose core structure was also subject of the research by Gross’ team is already in clinical testing.

Orchard Therapeutics allies with Oxford BioMedica

LONDON & Oxford, U.K.—Orchard Therapeutics, a biotechnology company dedicated to bringing transformative ex vivo gene therapies to patients with serious and life-threatening conditions, announced late November that it was also subject of the research by Huber.

Many gram-negative bacteria are pathogenic, including E. coli, Helicobacter pylori, Salmonella, Chlamydia pneumoniae and Shigella. Researchers have known for some time that infections can increase the risk of Alzheimer’s; however, this is the first time anyone has found increased levels of gram-negative bacteria antigens in Alzheimer’s disease brains and bacterial molecules associated with the disease pathology.

”Finding bacterial molecules in the brain was a surprise, and finding more in the Alzheimer’s brains was a great surprise,” said Frank Sharp, professor of neurology and senior author on the paper. “People have noted infectious agents in brains. These are the first bacterial molecules that are consistently found in all brains.”

These findings, the researchers say, highlight the need to further investigate how infectious agents impact Alzheimer’s. While discovering LPS and K99 in Alzheimer’s disease brain samples is a good start, researchers must study the role bacteria may play in the disease pathology. A proven link between bacterial infections and Alzheimer’s could offer new opportunities to prevent and treat the disease.

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“We detected these bacterial components in aging brains,” said Zhao. “Our next step will be to work out if this is the cause or the consequence of Alzheimer’s disease. Do gram-negative molecules cause the disease, or is it that when people get Alzheimer’s more bacterial molecules get into the brain?”

LATE-BREAKING NEWS

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