MicroRNA inhibitors halt cancer cell growth

TSRI research says small-molecule RNA inhibitors can target and kill specific types of cancer

BY MEL J. YEATES
JUPITER, Fla.—In early March, scientists at the Disney Lab of The Scripps Research Institute (TSRI) announced they had designed two new drug candidates to target prostate and triple-negative breast cancers. The new research, published recently as two separate studies in ACS Central Science and the Journal of the American Chemical Society, demonstrates that a class of drugs called small-molecule RNA inhibitors can successfully target and kill specific types of cancer.

“This is like designing a scalpel to precisely seek out and destroy a cancer—but with a pill and without surgery,” said Dr. Matthew D. Disney of the Department of Chemistry at TSRI’s Florida campus, who was senior author of both studies. In their ACS Central Science study, Disney and his colleagues used DNA sequencing to evaluate thousands of small molecules as potential drug candidates. The researchers were on the lookout for molecules that could bind precisely with defective RNAs.

This strategy led them to a compound which targets an RNA precursor molecule. Disney tells DDNews, “Targapremir-18a is a small-molecule drug that binds to a precursor to microRNA 18a. The compound inhibits the production of microRNA 18a, which is upregulated and causative of prostate cancer.”

The scientists found that mature microRNA-18a inhibits a protein that suppresses cancer. When microRNA-18a is upregulated, cancers just keep growing.

Disney and his team tested Targapremir-18a, and found that it could target microRNA-18a and trigger prostate cancer cell death, “Since microRNA-18a is upregulated in cancer cells and helps to maintain them as cancerous, application of Targapremir-18a to cancer cells causes them to kill themselves,” Disney said.

“Targapremir-18a was tested in cancer cells isolated from patients. The compound silences the microRNA selectively, and causes prostate cancer cells to go into apoptosis or programmed cell death,” Disney continues. “[Next] we are planning to test the

New treatment potential for some breast cancers

PARP inhibitors may be able to treat more breast cancer subtypes than previously thought

BY RACHEL FLEHINGER
HINXTON, U.K.—A team of British researchers has uncovered genetic indicators suggesting that a greater number of breast cancer cases than previously thought are treatable with existing PARP inhibitors. Scientists from the Wellcome Trust Sanger Institute and their collaborators determined that patterns of mutations—mutational signatures—in some breast cancers could change how clinical trials are designed in the future.

Researchers associated with the Wellcome Trust say that understanding how more people can benefit from PARP inhibitors could change how clinical trials are designed in the future.

PUTTING SOME MUSCLE BEHIND SMA TREATMENT

Preclinical trial of CK-2127107 shows improved muscle function in mouse models of spinal muscular atrophy

BY LORI LESKO
SOUTH SAN FRANCISCO, Calif.—Targeted toward developing a long-awaited, fast-acting treatment for spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) patients, Cytotherapeutics Inc.—in collaboration with Astellas Pharma Inc.—has announced that preclinical data showed CK-2127107 (also known as CK-107) led to increased muscle function in mouse models. The study bodes well for a treatment tailored for humans a few years down the road.

The CK-107 data, presented at the ISSCR 2017 annual meeting, bode well soon for humans suffering from that disease—and perhaps sufferers of amyotrophic lateral sclerosis as well.

Data on CK-107 indicate that the next-generation fast skeletal troponin activator improves muscle function in mouse models of spinal muscular atrophy, which could bode well for humans suffering from that disease—and perhaps sufferers of amyotrophic lateral sclerosis as well.

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Organs-on-chips: small market, gigantic promise

LYON, France—Pioneers started the development of organs-on-chips around 2000 but really accelerated only after 2010, thanks to government initiatives, substantial funding and rising awareness, according to Yole Développement. As noted by Sébastien Clerc, medical technologies analyst at Yole, “Currently worth a few million dollars, the emerging organs-on-a-chips market has the potential to become a multibillion-dollar market.”

In its new “Organs-On-Chips 2017” report, Yole explains the challenges linked to drug discovery and the limits of the current process. Yole’s analysts provide a detailed introduction about organ-on-chip technology and propose an overview of history from first developments to now, along with a presentation of main players and their respective technologies.

The combined organs-on-chips devices and services markets reached $7.5 million in 2016, and Yole presents different scenarios between 2017 and 2022, with between 38 and 57 percent compound annual growth rate (CAGR) projected for that period.

Yole notes that the size of the market is still small and has very few players already in the production and commercialization phase. Most companies are spinoffs from universities’ labs and are currently improving their organs-on-chips models through an iterative process with industrial players. Pharmaceutical and cosmetics companies are eager to test different organs-on-chips solutions to assess which technology is best suited for which type of experiment, but they are conservative and will need time to widely adopt the technology, Yole maintains.

Depending on the speed of adoption and the ability of organs-on-chips companies to overcome technical challenges and to upscale production, Yole’s analysts detail different scenarios from realistic to optimistic in which the market could grow at different CAGRs to reach between $60 million and $117 million by 2022.

“There is no doubt such technologies have the potential to become a multibillion-dollar market in the mid- to long-term future given the billions of dollars they could help the industry to save every year,” noted Clerc. Ethical concerns are one of the key factors driving the new market, as more than 100 million animals are used in laboratory experiments worldwide every year, Yole notes, and could be replaced by pieces of microfluidic technology.

Still, “Increased media coverage and significant enthusiasm from the technology developers should not hide the significant barriers to technology adoption,” said Marie-Victoire Villien, technology and market analyst at Yole. Meanwhile, industry and governmental agencies have placed huge expectations on a few developers of organ-on-chip technologies which were awarded substantial funding.

Yole’s MedTech team proposes an analysis of potential consequences if these players were to fail. However, it is highly probable that the investments will continue, with large pharmaceutical and cosmetics companies starting to use organs-on-chips.

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THE GROWTH OF ORPHAN DRUGS

LONDON, BOSTON & TOKYO—The “steady and inexorable” growth of the orphan drug market remains one of the prominent themes in the fourth edition of the “EvaluatePharma Orphan Drug Report 2017,” but what has changed in the past year, according to the report, is the increased scrutiny of the price of these life-saving products.

“The image of the plucky small biotech striving to develop treatments for the rare diseases largely ignored by Big Pharma is long gone. Instead, this year we again find Big Pharma dominating the sector.” Gayathri Kanika, a GBI analyst. 

And the pricing incentives are substantial, added Andreas Hadjivasiliou, report author and EvaluatePharma analyst. “Of the top 100 drugs in the U.S., the average cost per patient per year for an orphan drug was $140,443 in 2016, compared with $27,756 for a non-orphan, putting pressure on the industry to continue to generate innovations that justify the huge costs of treatments.”

Among the report’s prognostic highlights:
- Worldwide orphan drug sales to grow to $209 billion by 2022, for a compound annual growth rate of 11.1 percent, approximately double the overall prescription market growth.
- Orphan drugs set to be 21.4 percent of worldwide prescription sales by 2022 (excluding generics).

Asia-Pacific non-small cell lung cancer market to soar

LONDON—The non-small cell lung cancer (NSCLC) market in the Asia-Pacific (APAC) region will more than double from $3 billion in 2016 to $6.2 billion by 2023, representing a substantial compound annual growth rate of 10.8 percent, according to business intelligence provider GBI Research.

In a recent report the company states that this growth will follow the introduction of a number of premium therapies such as Yerovan and necitumumab. Immune checkpoint inhibitors, such as Opdivo and Keytruda, will also drive growth, with the former recently gaining approval in Japan, Australia and South Korea, and the latter approved only in Japan and currently undergoing Phase 3 trials in China, Australia and South Korea.

“Owing to strong clinical performances, immune checkpoint inhibitors will have a greater uptake than other second-line market entrants and will compete among themselves for market share in the APAC region.” Gayathri Kanika, a GBI analyst. 

Asia-Pacific non-small cell lung cancer market to soar
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Partnering on plants
PARIS—A partnership agreement was announced late March between Pierre Fabre Laboratories and biotech company SETUBIO within the framework of the Nature Open Library program, an original open-innovation initiative launched by Pierre Fabre to develop the therapeutic properties of the latter’s library of plants. The work will leverage SETUBIO’s high-throughput biological screening platform to identify new, pharmaceutically active molecules for human and animal health.

“This collaboration with SETUBIO confirms the relevance of our open innovation initiative, Nature Open Library, which is aimed at exploiting all the potential of our 15,000-plant collection. It enables us to envisage the discovery of new therapeutic uses of plant extracts in sectors corresponding to or complementing our major fields of research,” said Laurent Audoly, Pierre Fabre Pharmaceuticals’ R&D director.

Strong growth ahead for global drug discovery
DUBLIN, Ireland—Research and Markets has announced the availability of one of its latest reports, “Global Drug Discovery Market Forecast 2016-2024.” The report notes that globally, the drug discovery market is expected to nearly double within the aforementioned time period, growing from $34.0 billion in 2016 to $68.7 billion by 2024, a compound annual growth rate of 9.1 percent. The key drivers within this market are the prevalence rates of major health issues such as diabetes, genetics disorders, mental health disorders, cardiovascular and other diseases. An aging population, increased healthcare expenditure and increased lifestyle-oriented diseases and fatalities are the main drivers of growth in the market, while market restraints include delayed processes and increased regulatory hurdles. An aging population, increased healthcare expenditure and increased lifestyle-oriented diseases and fatalities are the main drivers of growth in the market, while market restraints include delayed processes and increased regulatory hurdles.

Company inks collaboration with Ono Pharmaceutical for oncology target drug leads
BY KELSEY KAUSTINEN
WALTHAM, Mass.—A multitarget drug discovery collaboration is now underway between X-Chem Inc. and Ono Pharmaceutical Co. Ltd., with a focus on cancer. Per the agreement, X-Chem will use its proprietary DEX libraries in search of new drug leads against a number of high-impact oncology targets, and Ono will have the option to license identified lead compounds and will assume responsibility for further development and commercialization of any resulting programs. Though no specific financial details were released, X-Chem will receive an upfront payment in addition to research and licensing fees, and also stands to receive additional payments tied to the achievement of preclinical and clinical development markers and regulatory milestones, as well as sales royalties.

“Ono identified X-Chem as the partner of choice for the generation of new drug leads for several high-priority targets in our portfolio,” said Dr. Hiromu Habashita, corporate officer and executive director of discovery and research at Ono. “We are excited to work...

Fastert than Prozac
UCSD researchers find GLO1 quickly alleviates depression in mice
BY LORI LESKO
SAN DIEGO—Scurrying to find a more effective and faster way to alleviate the debilitating symptoms of depression, researchers at the University of California, San Diego (UCSD) School of Medicine have discovered that inhibiting an enzyme called glyoxalase 1 (GLO1) relieves signs of depression in mice—and kicks in quicker than the antidepressant Prozac.

The UCSD study, published in the March 21 issue of Molecular Psychiatry, sets the stage for the researchers’ discovery of a completely new class of potentially faster-acting antidepressant medications.

“Depression affects at least one in six of us at some point in our lifetime, and better treatments are urgently needed,” says senior author Abraham Palmer, professor of psychiatry and vice chair for basic research at UCSD. “A better understanding of the molecular and cellular underpinnings of depression will help us find new ways to inhibit or counteract its onset and severity.”

Palmer notes that current treatments not only take weeks to reduce the symptoms, but at best are often only modestly effective and produce undesirable side effects.

“Developments of novel antidepressants have stalled, and many of the largest pharmaceutical companies have de-emphasized this area because they believe that the problem is too difficult to solve,” Palmer says. “A new class of antidepressants would be game-changing, especially if they were fast-acting and addressed some of the other shortcomings of currently available treatments.”

“We are currently working with medicinal chemists to develop better GLO1 inhibitors that would have a longer half-life and be orally available,” he adds. “Those drugs would have to be evaluated for safety in animal models and then in humans...
“This is our third partnership with a Japanese company in the last three months, signaling the broad global interest of the pharma industry in X-Chem’s DEX platform for finding novel drug leads.”

Dr. Rick Wagner, CEO of X-Chem

Prior to that, in mid-February, X-Chem expanded its collaboration with Janssen Biotech Inc., one of the Janssen Pharmaceutical Companies of Johnson & Johnson, for the discovery of new drug leads for treating inflammatory diseases. The original agreement began in December 2014, and this expansion will leverage the DEX platform to identify novel modulators for select disease targets, and comes after Janssen licensed several series of small molecules in 2016 that were discovered by X-Chem.

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“As X-Chem explained in a press release, “The library is screened as a mixture using affinity-based binding to a target of interest. Certain rare molecules in the library that bind to the target can be ‘fished out’ while the rest of the molecules are washed away. DNA sequencing methods are then used to detect molecules that are enriched when bound to the target. The diverse nature of the library produces multiple families or clusters of related molecules that bind to the target, forming a basis for emergent structure-activity relationships. Structure-activity relationships are typically used by medicinal chemists to guide iterative chemical maturation of a molecule into a drug.”

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excessive histone acetylation, an epigenetic process that regulates gene expression. More years of drug use correlate with higher levels of hyperacetylation.

The Mount Sinai study focuses on epigenetics, the study of changes in the action of human genes caused, not by changes in DNA code people inherit from parents, but instead by molecules that regulate when, where and to what degree genetic material is turned on and off. Histone acetylation of DNA linked proteins is an essential process for gene regulation by which an acetyl functional group is transferred from one molecule to another, thus activating gene expression.

To find the molecular basis of heroin addiction, the Mount Sinai team focused on the striatum, a brain region linked with drug addiction because of its central role in habit formation and goal-directed behavior. In postmortem human tissue from 46 heroin users and 37 controls, they found acetylation changes at genes that regulate the function of glutamate, a neurotransmitter that regulates the drug reward system and controls drug-seeking behavior. Changes were identified at the glutamate receptor gene GRIA1, which has been cited in drug use.

According to study leader Dr. Yasmin Hurd, professor of psychiatry and neuroscience at the Icahn School of Medicine and director of the Center for Addictive Disorders at the Mount Sinai Behavioral Health System, “We hypothesized that the epigenetic impact of heroin addiction on cellular processes at the Mount Sinai study site is transferred from one molecule to another, thus activating gene expression.

In an article in The Journal of Neuroscience, TSRI professor Marisa Roberto, senior author of the new study, said the findings could help researchers develop novel drugs. Using a rat model, researchers allowed rats to self-administer heroin and observed the same hyperacetylation alterations that were found in the postmortem human brains. Then the heroin-addicted rats were treated with JQ1, a compound originally developed against cancer. The compound inhibits the readout of acetylated epigenetic proteins, reducing accessibility to the DNA that was previously induced by heroin. The drug reduced heroin self-administration among study rats. Importantly, JQ1 also reduced drug-seeking behavior after abstinence from heroin, suggesting it might be beneficial for long-term heroin users. As Hurd explained, “Our findings suggest that JQ1 and similar compounds might be promising therapeutic tools for heroin use disorder. Furthermore, the animal model we created displayed analogous epigenetic alterations related to heroin use will be useful for future studies looking to identify addiction-related changes that translate to the human brain.”

She added that JQ1 had been used unsuccessfully for cancer in animal studies, showing that it was safe. In the Mount Sinai study, conducted along with researchers from Semmelweis University in Budapest, Hungary, the drug showed promise when self-administered. She hopes to bring it to clinical trials within a year.

In other unrelated substance use research, researchers have patented a compound originally developed against cancer that inhibits the readout of acetylated epigenetic proteins. The UC San Diego researchers have used a rat model to test the hypothesis that the enzyme GLO1 removes this byproduct, but inhibiting GLO1 can also increase the activity of certain neurons in the brain. The researchers found increased activity in both nondependent, or naïve, and alcohol-dependent rats. The researchers were surprised to discover that blocking the release of a neurotransmitter called GABA. Boosting these LTCCs reduced voluntary alcohol consumption in naïve rats. However, in alcohol-dependent rats, there was decreased abundance of LTCCs on neuronal cell membranes, disrupting their normal ability to drive a dose of alcohol’s effects on cerebral amygdala activity. Instead, increased neuronal activity was driven by a stress hormone called corticotropin-releasing factor (CRF) and its type 1 receptor (CRF1). By blocking the receptor, there is reduced voluntary alcohol consumption in the dependent rats.

Studying these two groups shed light on how alcohol functionally alters the brain, according to Roberto. She hopes the findings lead to better ways to treat alcohol dependence. The new findings suggest that doctors could analyze certain symptoms or genetic markers to determine which patients are likely to benefit from the development of a novel drug that blocks that activity.

UCSD researchers at the Icahn School of Medicine at Mount Sinai have found direct evidence of opiate-related epigenetic alterations in the human brain, along with a possible therapy: JQ1, a compound originally developed against cancer that inhibits the readout of acetylated epigenetic proteins. Pictured here is the Mount Sinai Medical Center.

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Lhasa and Optibrium enter research and product development collaboration

Drug discovery software specialists combine expertise to extend studies into drug metabolism modeling

By Donews Staff

Cambridge & Leeds, U.K.—Optibrium and Lhasa Ltd., developers of software for small-molecule property prediction, design and optimization, announced April 11 that they have formed a collaborative partnership to research next-generation drug metabolism modeling. Results from the work will be used by both organizations in the development of future products with improved and extended metabolism prediction capabilities.

Developing novel medicinal chemistry is a significant avenue of research and finds application in the development of drugs, cosmetics, nutritional supplements and agrochemicals. It is necessary to understand a compound’s pharmacokinetics and ensure that it has sufficient exposure at a target to exert its therapeutic effect. In addition, it is important to predict the formation of toxic metabolites, which contributes to the high attrition rates experienced in the development of new chemical entities, the imposition of black-box warnings or even the withdrawal of approved pharmaceuticals. Therefore, the ability to identify potential metabolite issues early is of crucial importance to improving the efficiency and safety of the drug discovery process, the partners say.

The research project has appointed Dr. Mario Oeren as senior scientist to head the study and work with a team of scientists from both Lhasa and Optibrium. A theoretical chemist who has specialized in computational chemistry, Oeren has a Ph.D. in natural sciences from Tallinn University of Technology in Estonia, where he has since worked as a researcher and lecturer. Mario will be based at Optibrium’s headquarters in Cambridge.

“This R&D collaboration with Lhasa builds on a long-standing relationship and is part of our continued investment in the development of novel technologies to improve efficiency in drug discovery,” said Dr. Matt Segall, CEO of Optibrium, “We welcome Mario to the team and look forward to extending the metabolism modelling capabilities within our combined product portfolio for the mutual benefit of Lhasa members and StarDrop users.”

Dr. Chris Barber, director of science at Lhasa, added: “We are excited by the complementary approaches that Lhasa and Optibrium have applied in the past, with Lhasa capitalizing on data donated by its member organizations and Optibrium applying theoretical approaches. Both approaches have their advantages, but combining and applying them across all stages of development should allow us to provide real benefit to the end user.”

In StarDrop, Optibrium says it has developed a comprehensive suite of integrated software with a highly visual and user-friendly interface, enabling a seamless flow from the latest data through to predictive modeling and decision-making regarding the next round of synthesis and research, improving the speed, efficiency and productivity of the drug discovery process. Seamlessly connecting with other models, informatics methods and databases, StarDrop provides user-friendly access to resources, making project management quicker and simpler, according to the company.

Lhasa specializes in the development of transparent in-silico models together with supporting databases in the fields of toxicology, metabolism, degradation and organic synthesis. The company touts itself as a pioneer in the production of knowledge-based systems, and it notes that Meteor Nexus, an expert knowledge-based system for the prediction of metabolism, is used extensively within the pharmaceutical and related industries.

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StarDrop is an in-silico platform to test molecules against any form of RNA defect-related disease. The research project has appointed Dr. Mario Oeren as senior scientist to the study and work with a team of scientists from both Lhasa and Optibrium. A theoretical chemist who has specialized in computational chemistry, Oeren has a Ph.D. in natural sciences from Tallinn University of Technology in Estonia, where he has since worked as a researcher and lecturer. Mario will be based at Optibrium’s headquarters in Cambridge.

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BY RANDALL C WILLIS

I AM HE AS YOU ARE HE as you are me, and we are all together—unless we’re talking about cancer.

Although Eggem and Walinus didn’t factor highly into many of the talks featured at the AACR 2017 conference in Washington, D.C., last month, neither it seems did many people who weren’t Caucasians of European descent.

For whatever reason, people of African, Central and South American, Native American and Asian descents have not featured prominently in cancer research, and their absence may be leading to unacceptably poorer outcomes in the face of cancer, including higher death rates.

Access to care, largely tied to socio-economic status, has borne much legitimate blame in these outcomes.

High infrastructure diagnostic resources, life-saving biologics and long-term treatment regimens are not accessible to the majority of the world’s population. Similarly, living conditions often exacerbate economic disparities to a greater extent than risk factors simply not at play in much of North America and Europe.

But even in situations where the playing field is more even—such as between communities within the United States—the relative rates of some cancers and the likelihood of positive outcomes for Caucasian populations vs. other groups are quite heavily skewed in favor of the Caucasians.

As part of a larger AACR presentation on the need for diverse populations in cancer studies, Einar Krenny of Mount Sinai’s Icahn School of Medicine noted that certain groups have been almost completely excluded from consideration.

Citing the European Molecular Biology Laboratory data base, she noted that as of December 2016, almost 50 million subjects had participated genome-wide association studies (GWAS) globally, and yet 76 percent of those participants were identified as Caucasian, while another 20 percent were East Asians (a growing sector).

The remaining four percent, described as “Other,” largely comprised Africans and non-Caucasian peoples of the Americas.

Thus, in trying to correlate cancer with human genetics, how can we even begin to make headway while ignoring vast tracts of the global population?

In the same session, Case Western’s Kishore Guda described his group’s efforts to understand colorectal cancer (CRC) in the African-American population, where the disease occurs 25 percent more often and has 50 percent higher mortality than in non-Hispanic Caucasians. As Guda highlighted, since 1960, the research on CRC has dropped 39 percent in Caucasian-American men but increased 28 percent in African-American men, and the latter group consistently performs more poorly in clinical trials on Stage II and III CRC.

To better understand what was happening, Guda’s group set out to study the mutational landscape of CRC in African-Americans, noting that in four major CRC sequencing studies, only two of 33 CRC’s examined were from African-American patients.

From an initial analysis of almost 3700 protein-altering mutations across more than 2100 genes, the researchers narrowed their focus to 25 mutations that occurred predominately in African-Americans versus Caucasian-Americans (41 vs 15 percent; PNAS), and each of which led to poorer outcomes in Stage I to III CRC patients (JNCI).

Of the 25, four mutations were completely specific to African-Americans.

Further work is required to determine whether these mutations predominate in other populations and/or can serve as markers and possibly act as mediators of adverse outcomes in African-American populations.

These presentations were just two of several that highlighted the challenges of understanding cancers through a relatively monoclonal lens. Slowly, the scientific community is starting to shine light on these issues, as exemplified by efforts such as the 1000 Genomes Project, designed to broadly catalogue human genetic variation across the genome.

But in this so-called Era of Precision Medicine—and I will continue to describe it as so-called until I see a systematic approach to molecular analysis in clinical trials and drug discovery—it is unconscionable that we, how...
Our years after the CRISPR/Cas9 technology took the field of mouse genetics by storm, it is time to draw some initial conclusions about how the technology has performed and discuss some future developments already in sight. CRISPR/Cas9 is a gene-editing technology based on the ability of introducing a double-strand break in selected regions of the genome and exploiting the DNA repair mechanisms to modify the targeted sequence. By introducing the genetic modification directly in embryos and bypassing the embryonic stem (ES) cell stage, CRISPR/Cas9 represents a faster and cheaper way to provide researchers with its in-vivo models they need. Compared to other pre-existing gene editing tools such as Zinc Fingers and TALENS, CRISPR/Cas9 owes its success to its simplicity and robustness, as thousands of scientists around the world can testify. Simplicity and robustness are, however, not enough when it comes to selecting a genome-editing tool on its own, and, as every technology used to modify the mammalian genome, CRISPR/Cas9 needs to be specific, efficient, reproducible and flexible. Specificity In the initial days of CRISPR/Cas9, a major concern was that the system might not have been specific enough to be of much use to geneticists, due to its tendency of modifying unrelated sequences in the genome. Initial reports claimed that CRISPR/Cas9 could induce double-strand breaks not only in the specific target sequence, but also in many different genomic locations. These lesions were referred to as “off-target events.” Because of these observations, mouse geneticists were concerned that the modification of the off-target sites would result in secondary phenotypes in their models, and that the effort to segregate the unwanted mutations once the model was ready would nullify the advantages of using the technology in the first place. It turned out that the worries of off-target modifications had been exaggerated and off-target events were exceedingly rare when the technology was used to modify the mouse embryo. Although the scientific community is still collecting data on CRISPR/Cas9 and it is premature to make a definitive conclusion about its specificity, it is possible to state that off-target events do not represent a major concern when using this technology to modify the mouse genome. Efficiency The use of CRISPR/Cas9 to modify the mouse genome directly in the fertilized oocyte is today the standard approach for the use of this technology. Options to genomic manipulation of ES cells, gene editing in embryos does not allow any kind of selection of the desired event, implying that it must occur with very high frequency. In other words, if the desired modification event occurs in 10 percent of cases, one will need to modify 100 oocytes to obtain one single founder. On the other hand, if the frequency of the event is 1 percent, one must modify 100 embryos to obtain one correct founder. A major effort has therefore been devoted to increase the efficiency of the on-target modification, while paying attention to the described result by the main obstacle toward the transfer of a new technology from a single research laboratory to a wider audience. Lack of reproducibility is often an aspect of the intrinsic fragility of an experimental system (e.g., extreme sensitivity to pH or temperature conditions) making it impossible to apply the new process to a pipeline requiring a consistent performance. Arguably, the major strength of CRISPR/Cas9 is its reproducibility, resulting in an impressive record of reports of its successful use by many different laboratories just a few months after the original publication appeared. Robustness of CRISPR/Cas9 is now widely recognized as one of its principal characteristics and, when properly designed, it is quite rare that a genome modification project based on this technology is not successful. Reproducibility Reproducibility is a key feature in every technology that is applied on a large scale by the scientific community. The inability to reproduce the described result by the scientific community. The inability to reproduce the described result by the focus of a score of laboratories worldwide. 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Modifying the mouse genome: Where are we now? The advent of the CRISPR/Cas9 technology has changed mouse genetics. By decreasing prices and reducing timelines for the generation of novel models, CRISPR/Cas9 has allowed many researchers to exploit the experimental power of in-vivo systems without investing the extensive resources previously required for obtaining the necessary tools. The possibility to modify directly the embryonic genome without the requirement of using ES cells has opened new model generation approaches such as model refitting, namely the introduction of additional genetic modifications into well-established multi-allelic existing models or the modification of transgenic alleles in already characterized mouse lines. Moreover, the ability of introducing an extensive range and rapid way specific point mutations in the mouse genome has already become a widely used tool to validate human genetic data obtained by clinical studies, providing an invaluable contribution to the field of human genetics. A new and exciting field is the in vivo screening of target genes by introduction of CRISPR/Cas9 elements via viral vectors, an application previously not conceivable with the standard tools of mouse genetics. Modifying the mouse genome: What’s next? CRISPR/Cas9 success in manipulating the mouse genome has raised very high expectations around this technology. In the past four years, however, it has become increas-ingly clear that CRISPR/Cas9 is very well suited for the introduction of relatively simple modifications. A way to overcome these limitations is to take a step back and use the technology to modify ES cells rather than embryos. The possibility of selecting thousands of independent ES cell clones allows the identification of rare events that might not be possible to identify when modifying directly the embryo genome. Although some of the intrinsic advantages of CRISPR/Cas9 are lost by bypassing the embryonic stem cell stage, it is possible to segregate the unwanted mutations once the model is ready would nullify the advantages of the system without compromising its many advantages. At the end, we must recognize that CRISPR/Cas9 is still in its infancy and that there is enormous room for further development. Due to the furious pace at which researchers around the globe are pursuing its optimization, it is likely that in a few years all genetic modifications will be introduced using CRISPR/Cas9 and that what is now considered not feasible might just become routine work in the near future. The first four years of CRISPR/Cas9 have been exciting, but the best is yet to come."
RESEARCH & DEVELOPMENT

BRIEFS

IL-33 signaling in severe allergy
SAN DIEGO—Biotechnology company AnaptysBio Inc. has reported that its collaborators at the Benaroya Research Institute at Virginia Mason (BRI) recently presented a translational research study at the AAAAI 2017 Annual Meeting. The study evaluated the biology of TH2A cells, a subset of T cells found in elevated numbers in patients with peanut allergies. These cells display increased sensitivity to IL-33 signaling due to higher expression of that cytokine’s receptor, and when stimulated with IL-33, TH2A cells express much higher levels of effector cytokines IL-4, IL-5 and IL-13, which are thought to be linked with severe peanut allergy. The study highlighted IL-33 as a key checkpoint for allergic responses and IL-33 blockade as a potential approach for reducing cytokine expression in cases of severe peanut allergy. AnaptysBio is advancing ANB020, its proprietary anti-IL-33 antibody as a treatment for severe adult peanut allergy, and is now enrolling patients in a Phase 2a trial.

More cellular options at Cellaria
CAMBRIDGE, Mass.—In an effort to offer more accurate patient- and disease-specific cell models, Cellaria LLC has announced that its service offerings now include a suite of stem cell services. The company’s new stem cell division will offer customers RNA reprogramming and differentiation services, with an initial reprogramming focus on custom solutions for primary cell establishment, induced pluripotent stem cell generation, banking and characterization, and customizable differentiation services for several cell types. “RNA reprogramming is a valuable and necessary tool for creating disease-specific cell lines for modeling,” said Cellaria CEO David Deems. “It is also increasingly being identified as a mechanism of tumor plasticity. We are genuinely excited to add a comprehensive suite of stem cell services and begin exploring the intersection between stem cell and cancer models.”

Potential colon carcinoma cure
Small-molecule compounds demonstrate tumor regression and adaptive immune response
BY ILENE SCHNEIDER
SEATTLE—Kineta Inc., a biotechnology company focused on the translational development of novel therapies in immuno-onco-logy, presented on a poster at the discovery and characterization of small-molecule compounds that appear to provide adaptive immune response and tumor regression on March 22 at the Keystone Symposia on Molecular and Cellular Biology conference titled “Cancer Immunology and Immunotherapy: Taking a Place in Mainstream Oncology.”

Kineta is a sustainable biotech company that advances therapies from discovery to clinical proof of concept and actively collaborates with private, government and industry partners to advance research in chronic pain, immuno-oncology and infectious diseases. The “hit to lead” small-molecule compounds activate interferon response factor 3 (IRF3) via RIG-I-like receptor (RLR) pathways and demonstrate immune-mediated tumor regression in a murine colon carcinoma mouse model, according to the company. Additionally, mice in the study that demonstrated complete tumor regression to initial drug treatment were resistant to tumor re-challenge, confirming an adaptive immune response.

New hope might be on the horizon for patients with colon cancer if data regarding Kineta’s RLR agonists in mouse models translate over to humans.

A CNS collaboration
nLife, WAVE Life Sciences team up for the first time on nucleic-acid therapeutics
BY KELSEY KAUSTINEN
GRANADA, Spain—nLife Therapeutics S.L and WAVE Life Sciences Ltd. have collaborated on a research collaboration to investigate cell-specific targeting of nucleic-acid therapeutics in the central nervous system (CNS). The collaboration will run the next two years, with the companies working to determine if certain chemical moieties are capable of directing the distribution and uptake of nucleic acid cargo to different cell types such as neurons, glia and astrocytes. Though specific financial details were not disclosed, WAVE will be funding the related research activities at nLife and will have an option.

As good as the real thing?
Organovo shares bioprinted kidney tissue data and celebrates review of their bioprinted liver tissue
BY MEL J. YEATES
SAN DIEGO—Organovo Holdings Inc., a 3D biology company, has announced the publication of data in Frontiers in Physiology showing that its 3D bioprinted proximal tubule tissue model exhibits key characteristics of renal physiology that allow for in-vitro kidney toxicity testing. In addition, Organovo noted a recent article published in the ILAR Journal. The publication explored new technologies that could reduce both dependency on animal models and occurrence of liver toxicity in clinical trials, and provides a thorough review of human tissue models and how they can accelerate drug development across all discovery stages, including Organovo’s 3D bioprinted liver model.

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immune response in these animals. As Kineta CEO Shawn Iadonato explained, “Tumors exist in an immunosuppressive environment and have many strategies of immune evasion. Kineta’s RLR agonists redirect the immune system to break tumor tolerance and elicit novel antigen-specific T cell responses. These data are groundbreaking in cancer immunotherapy as we successfully established tumor immunity in mice that had complete regression to an initial tumor.”

He added that in this study, Kineta’s novel small-molecule compounds demonstrated two immunomodulatory activities. First, they stimulate the RLR/IRF3 pathway in myeloid cells to induce the secretion of inflammatory chemokines/cytokines by human peripheral blood mononuclear cells and dendritic cells. Second, they induce immunogenic cell death (ICD) in the CT26 colon carcinoma model. Inducing ICD in tumor cells results in the release of danger signals including ATP, HMGB1 and calreticulin that eventually enhance immune recognition of the tumor.

“In turning a cold tumor hot, we believe that Kineta’s RLR agonists can work in synergy with other immunotherapies like checkpoint inhibitors to potentially enhance efficacy and patient survival.” Kristin Bedard, vice president of R&D at Kineta

including ATP, HMGB1 and calreticulin that eventually enhance immune recognition of the tumor.

According to Kristin Bedard, vice president of research and development at Kineta, “When ICD is elicited in tumor cells, they activate ‘kill-me’ markers such as ATP, HMGB1 and calreticulin. The immune system recognizes these markers and initiates an antitumor response. In turning a cold tumor hot, we believe that Kineta’s RLR agonists can work in synergy with other immunotherapies like checkpoint inhibitors to potentially enhance efficacy and patient survival.”

Kineta just unveiled its immune-oncology program in October. Around that time, Iadonato joined a panel of leaders from other biopharmaceutical companies to discuss novel new treatment strategies in immunology. The panel presentation entitled “The Intersection of Inflammation and Immuno-Oncology: Risks and Opportunities” was conducted at the 15th annual BIO Investor Forum in San Francisco. Iadonato highlighted details around Kineta’s small-molecule compounds that may activate the RIG-I pathway to elicit immunogenic cell death in cancer tumor models. These novel compounds were identified using Kineta’s proprietary AViiD screening platform, which has also identified innate immune antivirals and vaccine adjuvants.

“Cancer is typically not recognized as foreign by the body’s immune system, which allows tumors to grow unchecked,” Iadonato explained. “Kineta’s immune modulators activate the RIG-I pathway and may reprogram the immune system to recognize tumors as foreign and elicit neoantigen T cell responses to kill cancer. Priming the tumor microenvironment may also enable other therapies to be more effective when used in combination.”

In recent news of other therapeutic areas for Kineta, the company presented a talk at the 9th Annual Biotech Showcase Investor Conference in San Francisco in January. Iadonato provided an overview of the company and KCP-400, a novel non-opioid in preclinical development for the treatment of chronic pain. He outlined the robust analgesic, anti-inflammatory and neuroprotective effects that have been demonstrated in multiple pain models with this first-in-class therapeutic.
ORGANOVO

CONTINUED FROM PAGE 12

“Both liver and kidney drug toxicities are significant challenges for pharmaceutical companies working to advance safe and effective therapies,” said Keith Murphy, CEO of Organovo. “Previous validation data of our 3D bioprinted human liver tissue, combined with the data published in the peer-reviewed journal Frontiers of Physiology, on our 3D bioprinted kidney proximal tubule tissue clearly show that Organovo’s technology can address the unmet needs of our pharma customers and partners by providing timely, cost-effective and more accurate human tissue models for evaluating drug toxicity and drug-induced fibrotic disease.”

According to Dr. Deborah Nguyen, senior director of research and development at Organovo, “The ExVive 3D Bioprinted Kidney Tissue was commercially launched in 2014 and has demonstrated its potential to assess drug-related injury and fibrosis. The ExVive 3D Bioprinted Kidney Tissue was commercially launched in 2014. Organovo’s bioprinted kidney tissues provide a more accurate and reproducible model of human proximal tubule injury, allowing the investigation of multiple mechanisms of nephrotoxicity as well as renal disease.”

“Bioprinting is an automated process that places cells and cell-containing materials in precise locations in three-dimensional space so the cells naturally take on the shape and structure of native human tissue,” adds Nguyen. She says this 3D arrangement is achieved by generating multilayer building blocks—bio-ink—from the cells that will be used to build the target tissue. “[With] kidney tissue, three renal cell types are used to reconstruct the proximal tubule portion of the nephron. Those cell types are renal fibroblasts, endothelial cells and polarized human renal proximal tubule epithelial cells. The bio-ink building blocks are dispensed from a bioprinter, using a layer-by-layer approach, very similar to building a model with LEGO blocks.”

We expect to see a growing use of our kidney tissues in the coming years to model chronic kidney diseases. Cross-disease study platforms will help identify new therapeutic targets and biomarkers.”

She couldn’t disclose specific compounds currently being tested with the company’s pharma partners, but Nguyen says several compounds have been tested in proof-of-concept studies. In one of those studies, the Organovo team demonstrated induction of toxicity following treatment with the nephrotoxic antibiotic. Results showed a loss of tissue viability and epithelial cell function in a dose-dependent fashion. This effect was blocked by cimetidine, a compound that prevents chloride uptake via the transporter OCT2.

“In addition, work in partnership with colleagues from La Jolla Pharmaceuticals was presented at the recent Society of Toxicology meeting, showing the ability of the kidney tissues to model gentamicin-induced toxicity,” she says.

“The kidney is a complex organ, and there are clinical trials underway to study the proximal tubule that are sensitive to drug-induced toxicity. To try and develop a model system to look at other regions of the nephron, we have formed a collaboration with Prof. Melissa Little from the Murdoch Children’s Research Institute. Little and her team have demonstrated the ability to grow ‘mini-kidneys’ from induced pluripotent stem cells. We have licensed this technology in the hopes of developing a robust in-vitro system for investigating toxicity and disease pathways across the nephron. With Little’s incredible knowledge and success in kidney development combined with our bioprinting technology, the teams are working to develop an architecturally correct kidney for potential therapeutic applications,” Nguyen concludes.

EDITCONNECT: E051710

CNS

CONTINUED FROM PAGE 12

to license the latter’s technology for development and commercialization rights across the WAVE portfolio.

Following promising broad distribution of our existing CNS programs, and as we expand our portfolio into additional neurological disorders, we are exploring the ability of various technologies to selectively target certain cell types. This collaboration reflects WAVE’s long-term commitment to neurology and we expect will complement our oligonucleotide expertise within the CNS space,” said Dr. Paul Bolno, president and CEO of WAVE. “We are excited to initiate this research collaboration with nLife, a company that we believe is at the forefront of neuronal targeting technologies.”

Oligonucleotides are short nucleic acid polymers engineered to bind to specific complementary messenger RNA strands promoting their degradation. This in turn causes a decrease in the levels of specific proteins that may lead to diseases when they accumulate. By attaching small-molecule chemical ligands to oligonucleotides, it is possible to enable cell-specific delivery. In addition, conjugated oligonucleotides can be linked to un-druggable target proteins.

Andrés Montefeltro, senior vice president, Research, and founder at nLife, notes: “There is good synergy in combining our targeted neuronal delivery approach with WAVE’s stereopure oligonucleotide chemistry for development of gene-silencing therapeutics for the treatment of CNS disorders,” says Andrés Montefeltro, senior vice president of research and founder at nLife.

“Crossing the BBB [blood-brain barrier] is a big issue that has attempted to be addressed by nanoparticle formulations and antibody conjugates. However, using these technologies enables cell-specific delivery. In addition, conjugated oligonucleotides can cross the BBB with success, and a high systemic exposure remains unsolved.”

In an effort to get around this, “nLife’s approach is to selectively target disease affected cell populations rather than massive transfusion along the brain. We believe that cell-specific delivery can increase the therapeutic margin, reduce the treatment dose and minimize the toxicity and side effects,” he explains.

Where the partnership with WAVE comes in.

“nLife has developed a unique delivery platform for small oligonucleotides to target specific neuronal populations. We use small-molecule drugs that interact with selected receptors or transporters on the cell membrane of the target cell. This combination of a small-molecule drug linked to an oligonucleotide facilitates intracellular delivery into targeted neuronal populations of interest for the treatment of specific neurodegenerative diseases,” explains Montefeltro. “WAVE has a leading edge and strong proprietary position in chemistry for stereopure oligonucleotides for gene silencing. They can also target single point mutations in a mRNA with unprecedented results.

“There is good synergy in combining our targeted neuronal delivery approach with WAVE’s stereopure oligonucleotide chemistry for development of gene-silencing therapeutics for the treatment of CNS disorders.”

“By combining WAVE’s stereopure molecules with our targeted delivery technology, we believe it will be possible to address genetic diseases that were previously not accessible and potentially expand development of safe and effective treatments for a host of CNS disorders,” said Errol De Souza, executive chairman of nLife.

In other news for WAVE, the company announced a share offering in mid-April of 4.2 million shares at $24 each. Approximately $95.4 million is expected in net proceeds, and there will be a 30-day option for underwriters to buy up to an additional 625,000 shares, which could bring in an additional $14.1 million. The company’s stock dropped roughly 12 percent following the news.

Maxx Chatsko wrote on The Motley Fool that this offering “will pad a strong end-of-2016 cash position of $150 million and greatly aid the effort to advance the first drug candidates from the company’s novel technology platform into clinical trials … the company is ramping up development of nucleic acid therapeutics targeting a wide range of rare genetic diseases. Despite their promise, nucleic acid therapies have struggled to advance in the clinic due to complex synthesis methods—something WAVE Life Sciences claims to have solved with its novel chemistry platform that focuses on rational design. Proof-of-concept studies have demonstrated the approach results in more stable, active and specific therapeutic candidates than previous synthesis methods.”
Pharnext announces R&D agreement with Galapagos to generate a new pipeline of synergistic drug combinations

BY DDNEWS STAFF

PARIS—Pharnext SA, a French biopharmaceutical company developing an advanced portfolio of products in the field of neurodegenerative diseases, announced in March a research and development agreement with Galapagos NV. The main goal of this R&D deal is to generate an additional pipeline of novel synergistic drug combinations in a broad set of indications.

The agreement is based on both partners’ R&D capabilities, though the companies acknowledge that it will be heavily based on Pharnext’s disruptive technological platform called Pleotherapy. Until now, this platform has enabled the discovery and patenting of low-dose combinations of approved drugs repositioned in new indications and aims to develop more rapidly, safer and more efficacious treatments for unmet medical needs.

According to the partners, the collaboration agreement with Galapagos “highlights another outstanding feature of Pharnext’s platform: its ability to reinforce the potential of new candidate drugs.” More to the point: “For a given new preclinical or clinical candidate drug provided by Galapagos, Pharnext’s technology will aim to identify already approved drugs which could be combined at low doses with this new candidate in order to safely increase its efficacy.”

This agreement will not only concern therapeutic indications that were primarily envisioned by Galapagos, but also others that Pharnext will identify. Expanding their market to new indications as well as generating new patents should significantly increase the value of the new compounds, they say.

Pharnext’s approach is said to be applicable to a broad spectrum of diseases. Therapeutic indications that will be considered in this R&D agreement will notably include immuno-inflammatory and neurodegenerative disorders, both of which represent “potentially substantial markets.” Each of the companies will have priority on indications which will have been previously allocated.

“At Pharnext we have demonstrated that deeper understanding of genetics and molecular networks that underpin pathologies is key to drug discovery. The R&D collaboration with Galapagos validates the value of Pharnext’s innovative platform, Pleotherap- ry,” explains the technology, our team has already produced two novel synergistic drug combinations in late-stage clinical development. Moreover, this collaboration will enable our product portfolio with drug combinations including also new compounds,” said Dr. Daniel Cohen, co-founder and CEO of Pharnext. “We are proud to collaborate with Galapagos, an innovative and dynamic company in the biotechnology landscape. We look forward to working with Galapagos to generate new treatment options for patients who have no effective solutions today.”

“Pharnext has already obtained promising clinical results with its cutting-edge technology, which has encouraged us to collaborate,” added Onno van de Stolpe, CEO of Galapagos. “We are very pleased to collaborate with Pharnext and to benefit from Pharnext’s expertise in deciphering diseases’ molecular networks. We hope that this will reinforce Galapagos’ R&D capabilities to generate new therapeutic approaches in a highly efficient and modern manner.”

Intellectual property with regard to synergistic drug combinations generated by the R&D collaboration will be jointly owned by Pharnext and Galapagos. Financial terms of the agreement have not been disclosed.

In other recent Pharnext news, the French biopharma has announced that the first patients have entered the international Phase 3 extension study PLEO-CMT-FU of PXT3003 at La Timone University Hospital in Marseille, France. PXT3003 is Pharnext’s lead Pleodrug for the treatment of patients with mild-to-moderate Charcot-Marie-Tooth Disease Type 1A (CMT1A), a rare and debilitating inherited peripheral neuropathy for which there are no satisfactory approved treatment options available. Pharnext plans to apply for marketing authorization for PXT3003 in Europe and the United States in the first quarter of 2019. Long-term safety data from PLEO-CMT-FU would then be submitted to regulatory authorities during their review of the marketing authorization application. This should lead to PXT3003 market approval during the second half of 2019, as scheduled.

PXT3003 is an orally administered low dose synergistic combination of (RS)-baclofen, naltrexone hydrochloride and D-sorbitol, developed using the Pleotheraphy platform. In 2014, PXT3003 was designated an orphan drug for the treatment of CMT1A in adults in Europe and in the United States. “The initiation of this second international Phase 3 trial marks an important milestone for the whole PXT3003 clinical development program as it aims at confirming the long-term safety and tolerability profile of PXT3003,” said Dr. René Goedkoop, chief medical officer of Pharnext.

As for Belgian biotech Galapagos, another recent bit of news that was announced a new Phase 2 study investigating filgotinib and another investigational agent in cutaneous lupus erythematosus (CLE). This study is being led by filgotinib collaboration partner Gilead Sciences Inc.

“From the mutational signatures we were able to tell if they were caused by dysfunctional DNA repair proteins. When activated by DNA damage, these proteins recruit other proteins that do the actual work of repairing DNA.…”

BREAST

CANCER

Scientists from the Wellcome Trust Sanger Institute found that mutational signatures in some breast cancer tumors were similar to mutations found in people with malfunctioning BRCA1 and BRCA2 genes. This suggests that about 20 percent of breast cancer patients could benefit from PARP inhibitors currently used to treat BRCA1/BRCA2-related cancers.

In the UK-based study, researchers analyzed the breast cancer genomes of 1,560 patients and looked for every single type of mutation they possibly could. The team then developed a new computer-based tool called HRDetect able to discriminate between tumours with and without the BRCA1/BRCA2 mutation, based on the appearance of their genome. Cancer genomes without a mutation in the BRCA1 and BRCA2 genes are neat and organized, they say, whereas genomes with BRCA1/BRCA2-deficiency are chaotic.

HRDetect sees the tumor profile as if it is reading an X-ray, the researchers explain, and it can be applied across all tumors. The scientists discovered that many breast cancer patients had mutational signatures that were identical to people with faulty BRCA1 and BRCA2 genes, even though they had not inherited the BRCA genes. Indeed, they say, the data “clearly show a new mutational signature that is analogous to those seen in tumors with BRCA1/BRCA2 mutations.”

“We should explore if they could also benefit from the Wellcome Trust Sanger Institute,” Dr. Helen Davies, joint first author from the Wellcome Trust Sanger Institute, said: “From the mutational signatures we were able to spot many more tumours with defects in their DNA repair machinery that we couldn’t see before. This was only possible by sequencing the entire genome of these cancers. Further work needs to be done as there could be tumours with the same mutational signature elsewhere in the body that may respond to these drugs.”

The results were published in March in Nature Medicine and open up the possibility of one in five women being treated with PARP inhibitors, a class of drug previously only thought to be effective for women with an inherited BRCA1 or BRCA2 mutation. This would need to be tested through a systematic clinical trial on a wider set of patients to see if they might also be responsive to the drugs, with participants being selected based on the mutational signatures of their tumor.

Sir Mike Stratton, director of the Sanger Institute, said: “This work uses mutational signatures to identify the complete set of cancers that will respond to certain drugs that are already known to be effective in a subset. To translate these results into treatments, further sequencing of cancer genomes and more clinical trials are urgently needed, but this is a most promising start.”

PARP inhibitors are a group of pharmacological inhibitors of the enzyme poly ADP ribose polymerase (PARP). Several forms of cancer are more dependent on PARP for DNA repair than regular cells, making it an attractive target for cancer therapy. PARP proteins are known as DNA binding and repair proteins. When activated by DNA damage, these proteins recruit other proteins that do the actual work of repairing DNA.

Under normal conditions, PARP proteins are released from DNA once the repair process is underway. PARP inhibitors have been designed to specifically treat tumors with faulty BRCA1 and BRCA2 genes in breast and ovarian cancers, and when prostate cancer is currently being investigated. They appear to work in two ways. For cancers that are BRCA1/BRCA2-deficient, PARP is an alternative DNA repair mechanism that the cancer cells can use to continue to work by blocking the PARP DNA repair mechanism in BRCA1/BRCA2-deficient cancer cells, so damaged DNA is not mended, leading to cancer cell death. In addition, PARP inhibitors act to trap proteins on DNA strands, which are more toxic to cells than the unrepaired single-strand DNA breaks that accumulate in the absence of PARP activity, indicating that PARP inhibition could be a useful strategy to improve clinical outcomes in a wide range of cancer types. R&D news.

In the past, clinical trials for PARP inhibitors have focused mainly on the [small percentage] of women with breast cancer related to faulty BRCA1 and BRCA2 genes. However, our study shows that there are many more people who have cancers that look like they have the same signatures and same weakness as patients with faulty BRCA1/BRCA2 genes,” says Dr. Serena Nik-Zainal, lead author from the Wellcome Trust Sanger Institute. “We should explore if they could also benefit from PARP inhibitors. The results suggest that clinical trials need to look at cancer patients who share the same genetic signature in their cancer. This could change how clinical trials are designed in the future.”

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

RESEARCH & DEVELOPMENT

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Heat reports ComPACT therapy data

Poster presented at AACR meeting shows positive data for combination immunotherapy

BY JENNIFER CLIFFORD

DURHAM, N.C.—Heat Biologics Inc. recently presented new preclinical data from its collaboration with OncoSec Medical Inc., focused on evaluating the combination of Heat's immunotherapy platforms with intratumoral electroporation (EP), at the American Association for Cancer Research (AACR) Annual Meeting with a poster entitled “Combined Intra-tumoral Electroporation and Allogeneic Vaccination of Gp96-Ig/Fc-OX40L Stimulates CD8+ T cell Cross Priming to Tumor-Specific Neoantigens and Enhances Anti-Tumor Response.” Data from the poster demonstrated the effects of an intratumoral plus vaccination approach in a preclinical mouse model of melanoma. Researchers combined EP of ComPACT DNA (expressing g96-Ig and Fc-OX40L) directly into a tumor, with the cell-based Combination Pan-Antigen Cytotoxic Therapy, or ComPACT, to test possible synergistic benefits of vaccination plus intratumoral injection versus separate administration of vaccine and OX40 agonist antibody. The results presented confirmed that this combination approach led to increased antigen-specific CD8+ T cells, enhanced anti-tumor response and improved overall survival compared to individual treatments.

Heat Biologics' highly specific T cell-stimulating therapeutic vaccine platform technologies—ImPACT and ComPACT—in combination with other therapies, such as checkpoint inhibitors, shows positive data.
HEAT
CONTINUED FROM PAGE 16
ors, are designed to address three distinct but synergistic mechanisms of action: robust activation of CD8+ killer T cells; engagement of the human immune system’s most potent weapons against cancer; and reversal of tumor-induced immune suppression; and T cell co-stimulation to further enhance patients’ immune response. Their goal is to implement this therapy in the simplest and most efficacious way possible and with the lowest possible toxicity.

Heat’s approach is an off-the-shelf product that does not require invasive surgery or the isolation of patient tissues, as is required for autologous vaccine technologies. The company’s Immune Pan-Antigen Cytotoxic Therapy, or ImPACT, is an engineered cell line designed to express a version of a naturally occurring heat shock protein known as gp96, transforming allogenic living cancer cells into powerful miniature osmotic pumps that continually secrete heat shock protein gp96 along with its chaperoned antigens. The protein gp96 is a “molecular warning system” that has evolved important properties as a natural defense against necrotic cell death, in order to alert the immune system to the presence and identity of dangerous pathogens. By developing cell lines to secrete an engineered form of gp96, this technology simulates the immune system’s natural abilities.

Clinical and preclinical results indicate that ImPACT Therapy generates a potent antitumor immune response that fights targeted tumors and keeps the body tumor-free even when re-challenged with the cancer. This novel live-cell vaccine approach is applicable to a wide array of viral infections, including HIV and HCV, and parasitic infections like malaria as well as cancer.

The CD8+ cytotoxic T cell specific nature of the ImPACT system predicts that it will be most useful in stimulating immune responses for diseases where actual cell killing is an important part of the therapeutic effect. Cancer, which is a disease of mutated cells, naturally becomes the first indication. ImPACT applied to cancer therapy contrasts in several critical ways to other cancer immunotherapy technologies.

Taking this technology a step further, ComPACT enables Heat to combine a pan-antigen T cell activating vaccine and a T cell co-stimulator in a single product, offering the potential benefits of combination immunotherapy without the need for multiple independent biologic products. Using ComPACT, the company has engineered new product candidates that incorporate various ligand fusion proteins targeting co-stimulatory receptors (OX40, ICOS, 4-1BB) into the gp96-Ig expression vector, resulting in a single product candidate that includes both a pan-antigen T cell-priming vaccine and a T cell co-stimulator.

Heat is exploring various co-stimulatory receptors that may synergize with gp96-Ig-based vaccines. Findings from studies using the ImPACT vaccine demonstrate that antibodies quickly distribute systemically and produce systemic effects, while ComPACT vaccine research shows a local secretion of Fc-OX40L, producing superior antigen-specific CD8+ T cells associated with an increase in memory precursor cells. Studies have showed improved survival in a mouse colon cancer model.

Heat is currently in the midst of a Phase 2 trial with HS-110 (viagene-pumatucel-L) in combination with an anti-PD-1 checkpoint inhibitor to treat patients with non-small cell lung cancer and a Phase 2 trial with HS-410 (vesigenurtacel-L) in patients with non-muscle invasive bladder cancer. In addition, Heat’s wholly owned subsidiary, Zolovax Inc., is developing therapeutic and preventative vaccines to treat infectious diseases based on Heat’s gp96 vaccine technology, with a current focus on the development of a Zika vaccine in conjunction with the University of Miami.

“This proof-of-principal study shows there may be benefit in combining our vaccines with an intratumoral approach to deliver the vaccine directly into the tumor to increase the coverage of tumor-specific shared antigens and neo antigen presentation,” said Dr. Jeff Hutchins, Heat’s chief scientific officer and senior vice president of preclinical development. “It opens up the possibility of pairing our ImPACT and ComPACT platform technologies with intratumoral approaches, which aligns with our strategy to advance new, synergistic immuno-oncology combinations to improve patient outcomes.”

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MAY 2017 || DDNEWS 17
From 2018 onward, Envigo expects to create between five and 10 new in-vivo and in-silico tests each year—a market demand fueled in part by changing regulatory environments.

“Envigo’s main goal is to keep abreast of these [regulatory] changes and ensure we can employ these technologies to the benefits of customers—and that can’t happen without advancing the science and technology of product development testing,” he concludes.

“Beyond that we have a very active ‘horizon scanning’ ethic where we look for assays that we can develop to progress Envigo’s ‘de-risking’ strategy—by this we mean the ability to offer assays which can be used early in development to investigate high-risk problem areas such as genetic toxicity, drug-drug interaction, drug-induced liver injuries, etc.”

According to Dr. Peiyuan Lin, HD Biosciences’ senior vice president of research and development services, “HDB offers a full range of in-vitro toxicity services including safety profiling panels (Safety Assess), as well as cardioxicity, hepatotoxicity, genotoxicity and cytotoxicity screenings. Luxcel’s growing portfolio of proprietary mitochondrial toxicity, bioenergetics and metabolism assays is highly complementary to our current offerings and provides early and effective identification of mitochondrial liabilities for our clients’ drug discovery programs.”

“HDB’s preclinical service brings its clients the most up-to-date and valuable assays and tools to advance the drug discovery process,” said Dr. Ian Hayes, commercial director of Luxcel. “This joint effort will leverage the extensive expertise and capabilities from both sides.”

Founded in 2002, Luxcel Biosciences was and is an award-winning provider of cost-effective, easy-to-use fluorescence-based in-vitro cell test kits targeting cell metabolism, bioenergetics and drug toxicity applications. HD Biosciences is a bioLOGY-focused preclinical drug discovery CRO with head-quarters in Shanghai and operations facilities in Beijing and San Diego. The company offers comprehensive research and development services to global pharma, biotech and biotech industries around target validation, plate-based pharmacology and hit identification and lead discovery, therapeutic antibody discovery and in-vivo pharmacology. The company currently collaborates with eight of the 10 largest pharmaceutical companies in the world and has established strategic partnerships with many to develop their preclinical services.”

“Envigo wishes to partner with any company and to align them to their portfolios,” said Dr. Mike Caulfield, president of Contract Research Services and Research Model Services in North America at Envigo, commented: “R2G2 is a genetically engineered potential humanization benefit, the model has wider commitment to expand the number of GEMs in our portfolio and provide researchers with new models that address limitations with other mice currently used for research in oncology and infectious disease. Radiotherapy sensitivity testing has proven this model to be highly sensitive, and flow cytometry has demonstrated that the immune profile is similar to the NSGTM model. R2G2 provides a translational research approach that will help customers to more accurately predict outcomes.”

“One of the main benefits of the R2G2 model is its ability to tolerate the effects of a wider range of radiation dosages. This helps researchers more closely simulate the treatment environments of cancer therapies, where patients receive combinations of chemos/immunotherapy and radiation. The model is highly immuno-deficient, due to the lack of the functional T, B and NK cells resulting from the Rag2 and Il2rg gene disruptions. The R2G2 also brings the benefit of reduced ‘leakiness’ when compared to several other models with the SCID mutations, whose immune systems regenerate as they age, forming new T cells.”

In addition to the experiments already completed, Envigo is currentlyvalidating the Rag2 model’s potential humanization benefits, the outcome of which will be announced in early summer.

“Envigo wishes to partner with anyone—customers and other labs—who have a viable, relevant project which meets the following criteria: it enhances their product development opportunities or those of the industry in general; it adds to Envigo’s toolbox of in-vitro assays which we can offer to customers; and it increases Envigo’s attractive-ness to (new) customers as a scientific partner,” says Burlinson.

Envigo is helping to define the non-animal technologies regulatory environment, with its scientists currently sitting on various OECD expert working groups. Envigo is also a market leader and influence groups focused on skin and eye irritation tests, technical groups that advise on the development and revision of in-vitro test guidelines and guidance documents, as well as the International Council on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) group. Envigo has also submitted published validation data directly to the OECD and to the European Centre for the Validation of Alternative Methods, by invitation.

“Envigo’s customers use an integrated approach of in-vitro and in-vivo testing in most instances. We support those efforts, as they are required to get the most accurate results and to comply with regulatory mandates. In-vitro testing is not necessarily all about replacing in-vivo approaches, although that is one of the great benefits of it,” continues Burlinson. “Until regulations change, particularly in the pharmaceutical industry relating to the number of species and the in-vivo statistical data required to get a drug to IND, in-vivo testing will be with us for some time. We remain active in developing new in-vitro and in-vivo testing to satisfy our customers’ needs for accurate and actionable data.”

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Envigo wishes to partner with any company and to align them to their portfolios. For more information, visit www.DDN-News.com
**CK-107**

CONTINUED FROM PAGE 1

March, show that this next-genera
tion fast skeletal troponin activator (FSTA) improves muscle function in mouse models of SMA.

“These data support our ongoing Phase 2 clinical trial of CK-107 in adolescent and adult patients with SMA,” says Dr. Fady I. Malik, Cytokinetics’ executive vice president of research and development. “The increased muscle force at submaxi
mal nerve stimulation frequencies in mice inform the potential for CK-107 to increase muscle func
tion in patients living with motor neuron dysfunction.”

Until a few months ago, “there were no therapies available to treat SMA,” Malik tells DDNews. “Spinraza (nusinersan) is the first approved therapy. This is a gene
directed therapy with a different mechanism than CK-107. The two drugs could potentially be complementary.”

Two additional clinical trials of CK-107 are planned to begin in 2017, one in patients with ALS and one in elderly subjects with limited mobility, Malik says.

In neuromuscular diseases such ALS (also known as Lou Gehrig’s disease) and SMA, patients experience progressive, often fatal, muscle weakness, Malik says. CK-107 has the potential to increase muscle force, power and the time to relieve muscle fatigue.

“There hasn’t been a therapy approved for ALS in more than 20 years,” he adds. “This is a huge unmet need.”

The company’s potential therapy for ALS is tirasemtiv—which, like CK-107, is intended to slow the rate of calcium release from the regulatory troponin complex of fast skeletal muscle fibers—and it is “the first investigational therapy to demonstrate an effect on slowing the decline of respiratory function in patients with ALS (in our Phase 2 trial),” Malik says. “Patients typi
cally die of respiratory failure.”

Tirasemtiv has been granted Orphan Drug Designation and Fast Track status by the U.S. Food and Drug Administration and Orphan Medicinal Product designation by the European Medicines Agency for the potential treatment of ALS.

“We are currently conducting a Phase 3 trial in patients with ALS which is aimed at confirming this finding and extending it to a longer period of time,” Malik notes.

In addition to the preclinical work with CK-107, Malik says Phase 1 trial work has shed light on the potential for the investiga
tional compound to increase mus
cle force. Results of three double
d-blind, randomized, placebo-con
trolled Phase 1 studies of CK-107 in healthy volunteers were presented in a poster at the 19th International SMA Researcher Meeting during the 2015 Annual SMA Conference. CK-107 has demonstrated phar
cological activity that may lead to new therapeutic options for diseases associated with muscle weakness and fatigue. In non
clinical models of SMA, a skeletal muscle activator has demonstrated increases in submaximal skeletal muscle force in response to neuro
tal input and delays in the onset and reductions in the degree of muscle fatigue.

CK-107 has now been the subj
cet of five completed Phase 1 clini
cal trials. In addition to a Phase 2 clinical trial in patients with SMA, Cytokinetics is collaborating with Astellas on the conduct of a Phase 2 clinical trial in patients with chronic obstructive pulmonary disease.

In 2015, Astellas and Cytokinetics formed a partnership focused on the research, development and commercialization of skeletal muscle activators, with the pri
mary objective to advance novel therapies for diseases and medical conditions associated with muscle impairment and weakness. Under the collaboration, Cytokinetics exclusively licensed to Astellas rights to co-develop and potentially co-commercialize CK-107.

In 2014, the two companies agreed to expand their collabora
tion to include certain neuromus
cular indications, including SMA, and to advance CK-107 into Phase 2 clinical development, initially in SMA.

The agreement was further amended in 2016 to provide Astel
las with exclusive rights to co-
develop and commercialize CK-107 and other FSTAs in non-neuromus
cular indications (including SMA and ALS) and other novel mecha
nism skeletal muscle activators in all indications, subject to certain of Cytokinetics’ development and commercialization rights. Cytoki
netics may co-promote and con
duct certain commercial activi
ties in North America and Europe under agreed scenarios.

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Panasonic Healthcare Corporation of North America
CRISPR/Cas9 gene-editing technology continues to make strides in life sciences

BY JEFFREY BOULEY

VEN IF you don’t know that it stands for clustered regularly interspaced short palindromic repeats, chances are that if you’re reading this magazine you know what CRISPR is, at least in general terms. Genome editing—or the promise of it, at least, before it became practical—has been a big draw for life-sciences research since even long before the Human Genome Project opened up so much of our own genetic information to study and decode. After all, when it comes to life sciences, it isn’t just about editing the human genome for health reasons, as making better animal models is a huge issue as well.

But getting back to CRISPR specifically, scientists in recent years have found out just how effectively they can take advantage of CRISPR’s natural ability to degrade sections of viral RNA and use CRISPR systems to remove unwanted genes from nearly any organism.

“Although CRISPR-Cas9 is the ‘celebrity’ CRISPR system, there are 19 different types of CRISPR systems, each of which may have unique advantages for genetic engineering. They are a massive, untapped resource,” according to biologist Gabriel C. Lander of The Scripps Research Institute (TSRI). “The more we learn about the structures of these systems, the more we can take advantage of them as genome-editing tools.”

As TSRI explains, for many bacteria, one line of defense against viral infection is CRISPR-Cas, which TSRI describes as “a sophisticated RNA-guided immune system” at the center of which is a surveillance complex that recognizes viral DNA and triggers its destruction.

And it is here that TSRI encourages you to envision bacteria and viruses locked in an arms race.

Because, as it turns out, viruses can strike back and disable this surveillance complex using “anti-CRISPR” proteins. The problem was that researchers had not been able to figure out exactly how these anti-CRISPRs work.

Researchers at TSRI, though, say that for the first time, they have solved the structure of viral anti-CRISPR proteins attached to a bacterial CRISPR surveillance complex, revealing precisely how viruses incapacitate the bacterial defense system.

The research team, co-led by Lander—the other half of that leadership being Blake Wiedenheft of Montana State University and the results having been published recently in Cell—discovered that anti-CRISPR proteins work by locking down CRISPR’s ability to identify and attack the viral genome. One anti-CRISPR protein even “mimics” DNA to throw the CRISPR-guided detection machine off its trail.

“It’s amazing what these systems do to one-up each other,” said Lander. “It all comes back to this evolutionary arms race.”

Using the high-resolution imaging tech-
# SPECIAL REPORT

**PR Therapeutics and Casebia will obtain infection platform from MaxCyte.**

CRISPR Therapeutics, the company’s joint venture with Bayer, has licensed its CRISPR/Cas9 gene editing platform from MaxCyte with the aim of developing CRISPR/Cas9-based therapies.

The report highlights the potential for Duchenne muscular dystrophy (DMD) research, mentioning the involvement of CRISPR Therapeutics and Casebia Therapeutics in developing CRISPR/Cas9-based therapies.

**Exonics Therapeutics launches**

Exonics Therapeutics Inc., a newly formed biotechnology company focused on developing gene editing technologies like CRISPR/Cas9 to permanently correct a majority of mutations causing Duchenne muscular dystrophy and other neuromuscular diseases, has announced its founding.

**EGenesis**

ID-MARCH SAW eGenesis, a biotechnology company focused on utilizing genome editing technology to make xenotransplantation a routine and lifesaving medical procedure, announce that it raised a $38-million Series A financing co-led by Biomatics Capital and ARCH Venture Partners, with participation from Khosla Ventures, Alta Partners, Alexandria Equities, Heritage Provider Network, Berggruen Holdings North America Ltd., Uprising and Fan Ventures.

Xenotransplantation is the process of grafting or transplanting organs or tissues to humans from other species, and it “holds vast potential for filling the tremendous medical need for healthy organs for transplantation,” eGenesis notes. In the United States alone, more than 118,000 people are in need of an organ transplant and 22 people die every day because a match is not available, according to the U.S. Health Resources and Services Administration.

“While some challenges remain, our founding team confidently aspires to create a world where patients don’t have to die waiting for an organ transplant,” said Dr. Luhan Yang, chief scientific officer and co-founder of the company along with Harvard Medical School geneticist Dr. George Church. “With this significant investment, we expect to leverage our powerful genome editing platform to create a pathway toward developing non-exclusive rights to commercial use of MaxCyte’s Flow Electroporation technology for use in developing CRISPR/Cas9-based therapies for hemoglobin deficiencies and severe combined immunodeficiency. “It is important we prepare for the future by securing our access to the leading ex vivo delivery solution for both clinical and commercial use,” CRISPR Therapeutics Chief Business Officer Samarth Kulkarni said in a statement.

MaxCyte’s technology enables transfection of a variety of cell types at high efficiency, the company said. CRISPR Therapeutics and Casebia said they will use the technology to transfact hematopoietic stem cells.

**CRISPR Therapeutics and Casebia Therapeutics have signed a licensing deal for a cell transfection platform from MaxCyte with the aim of developing CRISPR/Cas9-based therapies.**

Duchenne is a rare X-linked genetic progressive muscle disease affecting nearly 15,000 boys in the U.S. and more than 300,000 boys worldwide. There is no cure for Duchenne. Children with the disease start missing development milestones at age 3 and often lose their ability to walk by age 12. All Duchenne patients will suffer from reduced mobility and independence, and ultimately respiratory or cardiac failure results in a reduced life expectancy in the mid-20s.

**EGenesis’ goal**, according to the report, is to develop “a one-time therapy that provides lifelong benefit to Duchenne patients.” Dr. Eric Olson of Exonics and delivering a safe and effective xenotransplantation solution for patients in need. We hope to see xenotransplantation recognized as a viable resource in the medical community as soon as possible.”

To accomplish this goal, eGenesis is harnessing its CRISPR-based technology platform to deliver safe and effective human transplantable cells, tissues and organs, which are grown in pigs. The eGenesis approach is still in its early stages, but includes genomic engineering of pig cells, organ maturation and finally, successful organ transplantation.

**CRISPR Therapeutics licenses cell engineering platform**

In other business news of the CRISPR world, CRISPR Therapeutics and Casebia Therapeutics, the company’s joint venture with Bayer, have signed a licensing deal for a cell transfection platform from MaxCyte.

Under the terms of the agreement, CRISPR Therapeutics and Casebia will obtain immediate availability of the MaxCyte transfection platform.

**For more information, please visit [www.sigma-aldrich.com](http://www.sigma-aldrich.com)**

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nique called cryo-electron microscopy, the researchers discovered several important aspects of CRISPR and anti-CRISPR systems.

First, the researchers saw exactly how the CRISPR surveillance complex analyzes the genetic material of a virus to see where it should attack. Proteins within the complex wrap around the CRISPR RNA like a grasping hand, exposing specific sections of bacterial RNA. These sections of RNA scan viral DNA, looking for genetic sequences they recognize.

“This system can quickly read through massive lengths of DNA and accurately hit its target,” said Lander. If the CRISPR complex identifies a viral DNA target, the surveillance machine recruits other molecules to destroy the genome of the virus.

Next, the researchers analyzed how viral anti-CRISPR proteins paralyze the surveillance complex. They found that one type of anti-CRISPR protein covers up the exposed section of CRISPR RNA, thereby preventing the CRISPR system from scanning the viral DNA.

“These anti-CRISPR proteins keep the bacteria from recognizing the viral DNA,” Lander explained. He called these anti-CRISPR proteins “exceptionally clever” because they appear to have evolved to target a crucial piece of the CRISPR machinery that bacteria cannot mutate to avoid viral attacks because doing so would disable the entire CRISPR system.

They also noticed that another anti-CRISPR protein uses a different trick. Based on its location and negative charge, the researchers believe this anti-CRISPR protein acts as a DNA mimic, fooling CRISPR into binding this immobilizing protein.

The TSRI researchers believe this new understanding of anti-CRISPR proteins may eventually lead to more sophisticated and efficient tools for gene editing.

For example, anti-CRISPR proteins might factor into CRISPR systems as a way to move in to stop gene editing; conversely, degradation of anti-CRISPR proteins could trigger gene editing. In essence, this could allow for what amounts to an off/on switch for CRISPR gene editing.

Shutting it down

And with the TSRI team shifting from the arms race analogy to the on/off switch analogy, we can revisit a story we shared in the February issue, “A flick of the switch,” in which DDNews Managing Editor Kelsey Kaustinen wrote that researchers at the University of California, San Francisco (UCSF) had discovered a way to switch off the widely used CRISPR-Cas9 gene-editing system using newly identified anti-CRISPR proteins.

“This image shows how the CRISPR surveillance complex is disabled by two copies of anti-CRISPR protein AcrF1 (red) and one AcrF2 (light green). These anti-CRISPRs block access to the CRISPR RNA (green tube) preventing the surveillance complex from scanning and targeting invading viral DNA for destruction. Understanding this process could aid in refining CRISPR genome editing techniques.

This technology. “Cas9 isn’t very smart,” Bondy-Denomy said. “It’s not able to avoid cutting the bacterium’s own DNA if it is programmed to do so. So we looked for strains of bacteria where the CRISPR-Cas9 system ought to be targeting its own genome—the fact that the cells do not self-destruct was a clue that the whole CRISPR system was inactivated.”

Using a bioinformatics approach designed by Rauch, the team examined nearly 300 strains of Listeria, a bacterial genus famous for its role in food-borne illness, and found that 3 percent of strains exhibited “self-targeting.” Further investigation isolated four distinct anti-CRISPR proteins that proved capable of blocking the activity of the Listeria Cas9 protein, which is very similar to SpyCas9.

Additional experiments showed that two of the four anti-CRISPR proteins—which the researchers dubbed AcrIIA2 and AcrIIA4—worked to inhibit the ability of the commonly used SpyCas9 to target specific genes in other bacteria (such as E. coli) as well as in engineered human cells. Together, the results suggest that AcrIIA proteins are potent inhibitors of the CRISPR-Cas9 gene editing system as it has been adopted in labs around the world.

“The next step is to show in human cells that using these inhibitors can actually improve the precision of gene editing by reducing off-target effects,” Rauch said. “We also want to understand exactly how the inhibitor proteins block Cas9’s gene targeting abilities, and continue the search for more and better CRISPR inhibitors in other bacteria.”

More options for CRISPR and molecular biology

Early this year, reflecting its drive to provide innovative solutions to the genomics community, Integrated DNA Technologies (IDT) said it had become the first genomics company to develop and bring to market a complete ribonucleicprotein (RNP)-based Cpf1 CRISPR system. The Alt-R A.c. Cpf1 CRISPR System, the company said, “inherits the optimized, efficient, and cost-effective traits of IDT’s innovative Cas9-based system while taking advantage of Cpf1’s natural AT-rich target sequence preference and ability to make staggered cuts.”

In addition, IDT launched an associated range of CRISPR support tools to expand experimental options and capabilities for molecular biology researchers. The new tools extend the ease-of-use and performance of IDT’s Alt-R System through options for fluorescent visualization, enhanced nuclelease transfection, and genome editing detection.

Taken all together, the new expanded Alt-R range reportedly “breaks barriers to wider target spaces not addressable by Cas9 systems alone, and provides a level of flexibility in experimental design not previously possible.”

As IDT noted, CRISPR is now one of the most widely used tools for genome modification, and the new Alt-R System is said to already be overcoming the limitations of using sgRNAs in the RNP complex by enhancing editing efficiency and lowering toxicity. Now, in developing a complementary Cpf1-based system, IDT says it has opened up options for targeting AT-rich sequences.

“In the initial development of our Alt-R product portfolio, we improved on the natural Cas9 system through chemical modification of the guide RNAs to create a more active, safer, and cost-effective system, supported by our high quality and high throughput manufacturability capabilities,” said Mark Behlke, chief scientific officer of IDT. “Our work makes CRISPR more accessible, allowing researchers to work with a wider variety of genomes and to design more innovative studies that were simply not possible before now—and we will continue to support them as they do so.”

CRISPR and discovery work

But it’s not all about the editing. As Horizon Discovery Group plc and Fulcrum Therapeutics Inc. announced late last year, they have entered into a collaboration under which Horizon’s CRISPR-based screening platform will be used to identify novel targets for regulating gene expression. The program will initially focus on genetic diseases where no effective treatment option currently exists.

As Horizon noted generally, its CRISPR-based screening platform, sophisticated bioinformatics, and cell line libraries provide a novel and highly efficient way to examine the regulation of genes and their role in disease; more specifically in this collaboration, Horizon will apply its platform and extensive know-how to identify novel gene regulation targets for further exploration by Fulcrum for the development of next-generation therapies.

“This CRISPR-based screening promises to be a powerful tool for the identification of novel targets and the collaboration with Fulcrum demonstrates the potential for this technology to be used in areas outside of oncology,” said Dr. Darrin Disley, CEO of Horizon Discovery, adding: “This partnership confirms Horizon’s role as a preferred partner not only for established biotechnology and pharmaceutical companies, but also for startups looking for long-term collaborations rather than having to build in-house capabilities.”
BROWSING THE LIBRARIES

The beginning of this year brought news that Cellecta Inc. had received Phase II SBIR grant funds from the National Institutes of Health to advance development of CRISPR/Cas9 library technology—advances that could significantly improve the performance and increase the utility of genetic screens for disease studies.

The improved screening platform will include genome-wide human and mouse CRISPR libraries and incorporate innovative features, such as multiple expression of sgRNAs that result in more effective irreversible gene disruption, enhanced gene activation (CRISPRa) or gene inhibition (CRISPRi). These technology improvements will be made available to the research community and Cellecta expects this to lead to enhanced drug discovery in many therapeutic areas.

“The work we are carrying out supported by this Phase II grant will accelerate systematic identification of new drug and biomarker targets, as well as facilitate the development of more successful targeted therapeutics,” said Dr. Donato Tedesco, Cellecta’s director of research and development. “Functional genomics screening comes with its unique challenges. We look forward to meeting these challenges with a significant improvement in what is becoming a go-to technology—CRISPR/Cas9—which we hope will drive meaningful discoveries to benefit human health.”

The advanced CRISPR libraries reportedly will improve effectiveness of gene knock-out in CRISPR knockout applications, will increase promoter activation in CRISPRa and repression in CRISPRi applications for greater efficiency and will reduce off-target effects for greater specificity. The toolset editing system. The flexibility of Agilent’s SureGuide platform enables CRISPR-based functional screening for any application, from genome-wide knock-outs to fully customized, user-designed libraries.

As Agilent notes, the introduction of genome engineering tools based on CRISPR has rapidly accelerated research related to functional studies of complex diseases and drug discovery. Genetic screens using pooled libraries are typically performed to locate and identify genes that are involved in cellular response, such as in signaling pathways, or to discover the function of novel genes, the company adds, and the introduction of CRISPR-based tools has provided an opportunity to overcome the limitations of previous technologies used in functional screening.

As a key component in any CRISPR experiment, guide library quality and composition can affect all of the downstream segments of the workflow including screening effort, sequencing cost and false positive/negative identification—reportedly, SureGuide offers high-fidelity CRISPR guides alongside Sure-Vector cloning technology, which enable an optimal distribution of guides to be maintained across even the most complex libraries.

“The new libraries represent the first of several planned products in a CRISPR-focused portfolio, supporting every aspect of the CRISPR screening workflow all the way through analysis and hit validation,” said Herman Verrelst, Agilent’s general manager of the Genomics Solutions Division and Clinical Applications Division.

First of its kind in CRISPR RNA

Fall 2016 saw the arrival of the Dharmacon Edi-tR Human Druggable Genome crRNA Library from GE Healthcare’s Life Sciences business, which reportedly enables screening of nearly 8,000 individual targets with CRISPR-Cas9 gene knockout. The offering is said to be the first arrayed synthetic CRISPR RNA (crRNA) library of its kind, and the company says it helps provide in-depth insight into a range of wide-reaching biological questions, adding, “With an emphasis on characterized genes of interest in drug discovery, it offers a powerful screening resource to identify potential therapeutic targets.”

Arrayed screening lets researchers overcome the limitations of selectable or sortable assays that are required for pooled library screening. Edit-R Druggable crRNA Library delivers more detailed one-gene-per-well information by enabling high content and multiparametric assays to easily characterize complex phenotypes.

Good CRISPR libraries are a key part of turning ideas about CRISPR for human therapeutics and genome editing of non-human organisms into successful efforts.

Agilent’s SureGuide harnesses the company’s oligonucleotide synthesis platform to create CRISPR guide libraries that are a critical component of the CRISPR/Cas genome editing system. The SureGuide platform enables CRISPR-based functional screening for any application, from genome-wide knock-outs to fully customized, user-designed libraries.

SureGuide platform enables CRISPR-based functional screening for any application, from genome-wide knock-outs to fully customized, user-designed libraries.
Perturb-seq for CRISPR-based perturbations

CRISPR-based single-cell genetics platform enables rapid analysis of critical gene networks

CAMBRIDGE, Mass. & SAN FRANCISCO—Researchers from the Broad Institute of MIT and Harvard and from the University of California, San Francisco (UCSF) have developed a new method for performing high-throughput functional screening of complex genetic interactions and resulting phenotypes in single cells, which they have dubbed Perturb-seq.

The findings could greatly speed scientists’ ability to map gene interactions and responses to environmental stimuli to advance understanding of healthy gene networks and also how they go away.

Described in two co-authored papers in the Dec. 15 issue of Cell, one led by Broad Institute researchers and one led by UCSF researchers, the Perturb-seq platform uses single-cell RNA sequencing to measure the effects of many CRISPR-based perturbations on large numbers of cells. The method can be used in many experimental applications, such as exploring the functional impact of genetic risk factors from genomic studies more efficiently than has been previously possible, or looking at genes mutated in cancer cells. Working collaboratively, the Broad and UCSF teams used Perturb-seq to make new discoveries about, respectively, the immune response in dendritic cells, which act as a critical messenger within the immune system, and the unfolded protein response, a cellular stress pathway implicated in a number of neurodegenerative disorders, demonstrating the potential of this platform to yield insight on a variety of biological questions.

“In Perturb-seq, we combined pooled CRISPR screens with the information-rich readout of droplet-based single-cell RNA sequencing to give us a powerful tool that dramatically increases the scope of what we can learn from functional genomic screens about how circuits are wired inside cells,” said Aviv Regev, senior author of the Broad-led study and a Howard Hughes Medical Institute investigator. “In particular, we can understand how the whole is greater than the sum of its parts, that is, why perturbing two different genes together gives an effect that is different than perturbing each of them alone.”

“Perturb-seq brings two technological advances—CRISPR-based perturbations and massively parallel single-cell RNA sequencing—together in a way that we think will greatly speed our ability to understand how different genes that encode for the components of cells are normally wired together, and what goes wrong in human disease,” said Jonathan Weissman, a professor of cellular and molecular pharmacology at UCSF, a Howard Hughes Medical Institute investigator, and senior author of the UCSF-led study. “Functional genomics studies can shed light on the connection between genotype and phenotype, but we’d like to also understand the mechanistic relationships between the two,” added Arany Diüt, co-first author of the Broad-led study and a graduate student at MIT. “Looking at the RNA level is a great place to start.”

In the Broad-led experiments, researchers used CRISPR/Cas9 nucleases to cut DNA and inactivate genes for transcription factor proteins (TFs) involved in the immune response in dendritic cells, and to inactivate genes for TFs and cell cycle regulators in a cancer cell line. Perturb-seq accurately identified individual gene targets, gene signatures and cell states affected by the individual gene modifications and explored how these genes interact and depend on one another. In the UCSF-led experiments, researchers used CRISPR-based transcriptional interference (CRISPRi) to simultaneously repress up to three genes in a cancer cell line and to investigate the unfolded protein response (UPR), a well-known quality control pathway that senses stress in the endoplasmic reticulum, where many of a cell’s key proteins are made. The UPR detects errors in cells’ protein-production machinery and ensures that impaired cells self-destruct. 
Linking predictive biomarkers to clinical trials

BMS, Foundation Medicine focus on such markers as tumor mutational burden, microsatellite instability

BY MEL J. YEATES

NEW YORK & CAMBRIDGE, Mass.—Bristol-Myers Squibb Co. (BMS) and Foundation Medicine announced a collaboration in late March which leverages Foundation Medicine’s genomic profiling and molecular information solutions to identify predictive biomarkers such as tumor mutational burden (TMB) and microsatellite instability (MSI) in patients enrolled across clinical trials investigating BMS’ cancer immunotherapies. Biomarkers can be used to characterize a tumor and the tumor microenvironment, which may reveal immune-related mechanisms predictive of how a patient may respond to immunotherapy.

“Cancer immunotherapy is evolving rapidly, and biopharmaceutical companies and the FDA are working on a way to better match patients to the correct therapy,” said Dr. Jeff Hutchins, Heat’s CSO and senior vice president of preclinical development, commented in part that “Although this is a small sample size and a non-randomized trial, we believe that this is an encouraging sign that the combination may be more effective than checkpoint therapy alone and could provide therapeutic benefit to a majority of lung cancer patients who do not respond well to checkpoint monotherapy. We remain focused on enrolling new patients to better characterize the objective response rate, durability of the response and associated immune activity.”

Proteon adjusts PATENCY-2 trial

WALTHAM, Mass.—As the first quarter ended, Proteon Therapeutics Inc. shared its financial results for full-year 2016, as well as an update on its PATENCY-2 trial for vonapanitase. This trial is the second Phase 3 clinical study of the investigational drug, with results from the first Phase 3 trial released in December 2016. After reviewing data from that trial, Proteon entered discussions with the FDA regarding protocol for PATENCY-2, and made several changes, including reordering the trial endpoints by making secondary patency and fistula use for hemodialysis co-primary endpoints and increasing planned enrollment from 300 to 500 patients. In addition, given the talks with the FDA, Proteon feels that, pending statistical significance in PATENCY-2 for each co-primary endpoint, the PATENCY-2 data and data from other completed studies could form the basis for a Biologics License Application and remove the need for additional studies.

A quick antibiotic response

Paratek’s omadacycline shows promise as broad-spectrum treatment for community-acquired infections

BY RACHEL FLEHINGER

BOSTON—Paratek Pharmaceuticals Inc. recently unveiled promising results from a Phase 3 clinical study into the efficacy of its antibiotic, omadacycline, in treating community-acquired bacterial pneumonia (CAPD). When compared with the commonly prescribed moxifloxacin, “These findings add to the growing body of evidence to support the efficacy of omadacycline in serious acquired bacterial infections. In addition to pneumonia, we are studying omadacycline in skin infections and urinary tract infections,” Dr. Evan Loh, president, chief operating officer and chief medical officer of Paratek. Paratek is a biopharmaceutical company focused on the development of new antibiotics and innovative solutions to address antibiotic resistance.

“Some cancer centers today fail to efficiently match patients, or they don’t do it because of the complexity of the task and the need to have a team or whole groups of teams set aside to do that,” says Panna Sharma, president and CEO of CGI. “This is a task that we think is perfectly suited for artificial intelligence.”

Adding AI to the mix

CGI teams up with Mendel Health to better match patients with clinical trials

BY KELSEY KAUSTINEN

RUTHERFORD, N.J.—Current clinical trials often face issues when it comes to enrollment—particularly in the case of cancer, when trials seek patients with specific tumor types or mutations—and a great deal of that difficulty boils down to a lack of awareness on the patient end of the equation. In an effort to better match clinical trials with cancer patients, Cancer Genetics Inc. (CGI) and Mendel Health, an artificial intelligence company, have formed a strategic partnership to apply the abilities of Mendel.ai, Mendel Health’s deep-learning engine.

Though no specific details were released, the partners will work together to combine the capabilities of Mendel.ai with CGI’s disease-focused reports and testing results. CGI and Mendel Health estimate that early-access partners will be able to start using this system by the second quarter of the year, with a more extensive launch in the third and fourth quarters.

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Trial matching/AI

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THE NEW WAY TO THE HEART?

Analysis shows Novartis’ Entresto improves glycemic control in heart failure patients with diabetes
BY LORI LESK

BASEL, Switzerland—Aiming straight to the heart of the matter, Novartis recently released the results of a new post-hoc analysis showing Entresto (sacubitril/valsartan) tablets improved glycemic control in patients with diabetes and reduced ejection fraction heart failure (HFrEF), suggesting that Entresto is indicated to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (HF) in patients with chronic HF and reduced ejection fraction.

“This analysis suggests that, in addition to the proven heart failure benefits demonstrated in PARADIGM-HF, Entresto may also help tighten glycemic control among heart failure patients with diabetes.”

Dr. Scott Solomon, director of noninvasive cardiology at Brigham and Women’s Hospital

Entresto, introduced to the market in 2015, is a twice-a-day medicine that reduces the strain on a failing heart. Novartis has established the largest global clinical program in the HF disease area across the pharma industry to date. New analysis of the largest HF study was first presented March 18 at the American College of Cardiology Annual Scientific Session and later published in The Lancet Diabetes & Endocrinology.

“These results show that in addition to its compelling cardiovascular efficacy, Entresto may have important metabolic benefits for HFrEF patients with diabetes,” Vasant Narasimhan, global head of drug development and chief medical officer at Novartis, stated in a news release. “We are excited about these results and committed to improving our understanding of the benefits of Entresto in different heart failure patient populations.”

PARADIGM-HF is a randomized, double-blind, Phase 3 study evaluating the efficacy and safety profile of Entresto versus a placebo.

Eric Althoff, head of global media relations for Novartis (pictured here), says that the company has “established the largest global clinical program in heart failure (FortiHFy) with more than 40 active or planned clinical studies.”

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Foundation Medicine’s FoundationOne assay combines comprehensive genomic profiling with proprietary algorithms to measure biomarkers, including tumor mutational burden and MSI from its comprehensive genomic profile (CGP) assays.

When asked about plans and future goals of the collaboration, the Foundation Medicine spokesperson tells DDNews that they are still being confirmed, as the terms of the collaboration agreement have not yet been released.

BMS also appears to be doing well generally in the financial sector, thanks to its immuno-oncology (IO) efforts. According to Seamus Fernandez, Dr. Le-Yi Wang and Richard Goss at Leerink Partners, “We believe Bristol-Myers Squibb will meet or beat first quarter consensus sales of $4.74B. [Bristol-Myers Squibb]’s unique and concentrated position in IO, together with a rapidly developing and near fully owned IO pipeline, makes it the most attractive potential strategic asset in all of large cap pharma.”

CLINICAL TRIALS

For more information, visit www.DDN-News.com
entresto
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Enalapril (a widely studied ACE inhibitor) in 8,442 patients with HFrEF. The baseline characteristics showed the patients enrolled in the study were typical HFrEF patients with NYHA Class II-IV heart failure. PARADIGM-HF was specifically designed to see if Entresto could decrease CV mortality by at least 15 percent. Patients received Entresto or enalapril in addition to current best treatment regimen. The primary endpoint was a composite of time to first occurrence of either CV death or HF hospitalization.

Novartis’ new post-hoc analysis of PARADIGM-HF data demonstrates Entresto lowered levels of HbA1c (a measure of glycemic control) by 0.26 percent vs. 0.16 percent for ACE-inhibitor enalapril in heart failure with reduced ejection fraction (HFrEF) patients who also had diabetes.

The use of insulin was also reduced by 29 percent among patients taking Entresto compared to enalapril-treated patients, the analysis shows. Up to 40 percent of HFrEF patients have diabetes, which is associated with worse cardiovascular outcomes.

Heart failure is a debilitating and life-threatening condition that impacts more than 60 million people worldwide, and is the leading cause of hospitalization in people over the age of 65. About half of people with HF have HFrEF, meaning the heart does not contract with enough force, so less blood is pumped out. HF presents a major and growing health-economic burden that currently costs the world economy $108 billion every year, accounting for both direct and indirect costs. Also, diabetes “is a major risk factor in heart failure and is strongly linked to progression of the disease, putting heart failure patients at increased risk of hospitalization and death,” states Dr. Scott Solomon, director of noninvasive cardiology at Brigham and Women’s Hospital, a professor of medicine at Harvard Medical School and senior author of the publication. “This analysis suggests that, in addition to the proven heart failure benefits demonstrated in PARADIGM-HF, Entresto may also help tighten glycemic control among heart failure patients with diabetes.”

Eric Althoff, head of global media relations for Novartis, tells DDNews that the company has “established the largest global clinical program in heart failure (FortiHFy) with more than 40 active or planned clinical studies. These trials will improve our overall scientific understanding of heart failure and generate additional data on efficacy and real-world evidence with Entresto.”

“Diabetes is a major risk factor and a common comorbidity in heart failure,” he continues. “We are currently evaluating the results of this post-hoc analysis to determine whether additional studies would be beneficial to this patient population.”

An analysis was conducted of 3,778 HFrEF patients in the PARADIGM-HF trial who were diagnosed with diabetes or had a baseline HbA1c greater than or equal to 6.5 percent without a reported diagnosis at screening (98 percent of patients assessed had type 2 diabetes). The investigators compared the effects of Entresto vs. enalapril on glycemic factors.

Entresto lowered HbA1c levels—a measure of average blood glucose levels for two to three months after one year of treatment for HF—and this effect was sustained over three years of study follow-up. Also, new use of insulin therapy or oral diabetes agents was also reduced in the Entresto group.

The new analysis of the data suggest that cardiologists need to keep an eye on blood sugar levels in diabetic Entresto patients, in case their diabetes meds need adjusting.
and commercialization of innovative therapies applying novel tetracycline chemistry. According to their website, Paratek sees unmet need for a well-tolerated, broad-spectrum agent with intravenous (IV) and oral formulations that can be used in the empiric treatment of community-acquired infections. Such a broad-spectrum antibiotic can allow patients to transition from the IV to a bioequivalent oral, potentially allowing the patient to be discharged early. In an outpatient setting, there is the potential to start the patient on oral therapy and avoid a hospitalization altogether. Oral treatments at home reduce the inherent risks associated with IV therapy and are more convenient for the patient. In addition, being able to facilitate early discharge—or in some cases avoid hospitalization completely—provides a significant cost saving to payers.

Omadacycline is their first in a new class of tetracyclines known as aminomethylcyclines, with broad-spectrum activity against gram-positive, gram-negative, aerobes, anaerobes and atypical bacteria. In-vitro and in-vivo studies have shown omadacycline has activity against drug-resistant pathogens, including methicillin-resistant Staphylococcus aureus, penicillin-resistant and multi-drug-resistant Streptococcus pneumoniae, vancomycin-resistant Enterococcus species and extended spectrum β-lactamase producing enterobacteriaceae.

It is a once-daily oral and IV, well-tolerated broad-spectrum investigational antibiotic being developed for use as empiric monotherapy for patients suffering from serious community-acquired bacterial infections, such as acute bacterial skin and skin structure infections (ABSSSI), community-acquired bacterial pneumonia (CABP), urinary tract infections and other community-acquired bacterial infections, particularly when antibiotic resistance is of concern to prescribing physicians. The Phase 3 randomized, double-blind, multicenter study was designed to compare the safety and efficacy of IV to once-daily oral omadacyline therapy to moxifloxacin IV to oral for treating adults with CABP, a significant and serious health issue.

“We were fortunate in that enrollment in our CABP study progressed quickly. We initiated the trial in November 2015 and completed enrollment in January 2017,” asserts Loh. “This rapid pace of recruitment enabled us to report top-line data in April, rather than Q1, as we had originally projected.”

“Often in treating pneumonia, the prescribing physician doesn’t know what specific pathogen(s) caused the infection. That is why we designed omadacycline to be a broad-spectrum antibiotic to be used as empiric monotherapy at the time of diagnosis, not requiring a positive culture before initiation of therapy,” says Dr. Evan Loh, president, chief operating officer and chief medical officer of Paratek.

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With these data now in hand, we will pursue an NDA with the U.S. FDA. We intend to file as early as the first quarter of next year. After that, we will seek regulatory approval in the EU,” says Loh. “We are anticipating a Priority Review with the FDA, which, if approved, would put U.S. commercial availability at late 2018. In addition, we are committed to scientific transparency and will publish or present the data from this trial at future congresses or in journals so that prescribing physicians may understand the efficacy, safety and tolerability of omadacycline. Further, these data will outline the observed clinical efficacy against a broad-spectrum set of specific pathogens that it targets and how it functions in the lung in subjects with community-acquired pneumonia.”

Oh, and one more thing. Paratek is also exploring the use of omadacycline to treat cases of multidrug-resistant Staphylococcus aureus (MRSA) in the healthcare setting. And it’s not just about MRSA anymore—it’s about every antimicrobial-resistant pathogen. Omadacycline is currently being evaluated in a Phase 3 study in skin infections, satisfied the regulatory submission requirements for special protocol assessment with the FDA. Thus, it has been granted Qualified Infectious Disease Product designation and Fast Track status by the FDA for the target indication.

This Phase 3 study in pneumonia, along with the previously announced successful Phase 3 study in skin infections, satisfied the regulatory submission requirements for special protocol assessment with the FDA. Thus, it has been granted Qualified Infectious Disease Product designation and Fast Track status by the FDA for the target indication. With these data now in hand, we will pursue an NDA with the U.S. FDA. We intend to file as early as the first quarter of next year. After that, we will seek regulatory approval in the EU,” says Loh. “We are anticipating a Priority Review with the FDA, which, if approved, would put U.S. commercial availability at late 2018. In addition, we are committed to scientific transparency and will publish or present the data from this trial at future congresses or in journals so that prescribing physicians may understand the efficacy, safety and tolerability of omadacycline. Further, these data will outline the observed clinical efficacy against a broad-spectrum set of specific pathogens that it targets and how it functions in the lung in subjects with community-acquired pneumonia.”

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“Some cancer centers today fail to efficiently match patients, or they don’t do it because of the complexity of the task and the need to have a team or whole groups of teams set aside to do that,” says Panna Sharma, president and CEO of CGI. “This is a task that we think is perfectly suited for artificial intelligence—mining the scientific literature, mining the clinical trials data, picking out the criteria, sorting through the structured and unstructured data in the patient record as well as the data coming out of BGI. Mendel Health has a very focused deep-learning algorithm that performs better than anything else that we’ve seen, and it’s been trained by clinicians, by doctors.”

The National Cancer Institute estimates that less than 5% of cancer patients take part in clinical trials, despite the benefits of early access to novel, targeted therapies. Also, a national survey of more than 1,000 individuals conducted by ResearchAmerica reported that fewer than seven out of 10 healthcare providers talk to their patients about clinical trials.

“The world’s best cancer treatments are currently in trials, but that doesn’t assure that the patients that fit those trials are aware of their existence even after being identified as an eligible biomarker. Traditional navigation tools are no longer realistic as trials are becoming more selective and treatments are becoming both more complex due to combinations and more targeted,” noted Dr. Karim Galil, founder and CEO of Mendel Health. “By integrating Mendel’s proprietary AI technology, CGI is the first diagnostic company able to augment the oncologist’s decision making by continuously matching the patient’s data with emerging clinical trials, based on previous diagnostic tests and any shared clinical data or records.”

Sharma expects this approach to benefit those conducting clinical trials as well, because making it easier to identify the appropriate patients to accelerate recruitment, and even in planning trials by allowing researchers to evaluate if patients with certain biomarkers or tumor types are present in sufficient numbers.

“Emerging therapies, our knowledge of cancer and biomarker-driven insights are advancing extremely rapidly, and require a constant and vigilant technology-enabled approach to ensure that the best possible insights are made available to our patients and families,” according to Sharma. “Artificial intelligence has advanced and impacted nearly every industry, and we believe it has the promise to transform laboratory based medicine. In an era where there is tremendous need to advance the innovative new therapies in unfilled trials with precisely matched patients that thus these increasingly complex enrollment criteria, Mendel.ai offers a timely, high-impact and ready-to-deploy solution.”

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ISSCR celebrates 15th anniversary during annual meeting in Boston

ISSCR 2017 highlights new discoveries in stem cell research and progress toward clinical therapies

BY JEFFREY BOULEY

PROGRESS IN STEM CELL research and its translation to the clinic will be the focus of the International Society for Stem Cell Research (ISSCR) annual meeting from June 14-17 at the Boston Convention and Exhibition Center in Boston—during which the ISSCR will also celebrate 15 years of existence.

More than 4,000 stem cell scientists, bioethicists, clinicians and industry professionals from over 50 countries are expected to be there at ISSCR 2017 to share and discuss the latest discoveries and technologies within the field and how they are advancing regenerative medicine.

The ISSCR annual meeting is the world’s largest meeting focused on stem cell research, with a series of lectures, workshops, poster presentations and a dynamic exhibition floor with nearly 200 exhibitors. Presentations span the breadth of the field, including topics such as stem cells and cancer, disease modeling and organogenesis, gene editing and gene therapy, potential breakthrough therapies currently being tested in clinical trials and more.

“The annual meeting is an essential forum for all stakeholders in the field of stem cell research,” said ISSCR’s president, Dr. Sally Temple, in a news release about the meeting. “Discoveries are moving forward quickly, with developments that are changing the way we view and treat disease. That has tremendous implications, not only for scientists, but also for regulatory bodies, industry and patients.”

Before the start of the meeting itself, on June 13, a Public Symposium organized by the meeting co-sponsor, the Harvard Stem Cell Institute (HSCI), will be held at District Hall in Boston. The symposium, titled “Innovation, Incubation, Investment: The Landscape of Stem Cell Research in Boston,” will feature local leaders in the Boston stem cell community.

At the ISSCR 2017 exhibit hall, find all of the technology and business solutions that can help move your research and lab forward, the society says. Meet face-to-face with technical specialists, learn about new products, find suppliers for your lab’s needs and more. The exhibit area will be divided into pavilions to make it easier than ever to locate companies of interest to you—Technology & Suppliers, Therapeutic & Commercialization, Academic and Start-up Row. Pictured here is the exhibit area of last year’s annual meeting.

Also, two pre-meeting sessions on that same day are specifically targeted toward clinicians and scientists and those interested in bringing new therapies to the clinic. They are:

• The Workshop on Clinical Translation, “How to Get From the Bench to the Clinic: Practical Advice for Completing an Investigational New Drug (IND) Application,” will examine the process of preparing an applica-
ISSCR to recognize several in stem cell arena

CHICAGO—In January, the International Society for Stem Cell Research (ISSCR) announced its 2017 award recipients for the McEwen Award for Innovation, the ISSCR Dr. Susan Lim Outstanding Young Investigator Award, the ISSCR Tobias Award Lecture and the ISSCR Public Service Award. Awarders will be recognized at ISSCR 2017 in Boston.

• McEwen Award for Innovation: Dr. Elaine Fuchs, the Rebecca C. Lancefield Professor at The Rockefeller University and a Howard Hughes Medical Institute investigator
• ISSCR Dr. Susan Lim Outstanding Young Investigator Award: Dr. Jayaraj Rajagopal, the Department of Internal Medicine at the Center for Regenerative Medicine of Massachusetts General Hospital and an associate professor at Harvard Medical School, as well as a Howard Hughes Faculty Scholar
• ISSCR Tobias Award Lecture: Dr. John Dick, Canada Research Chair in Stem Cell Biology and senior scientist for the University Health Network of Canada, as well as a professor at the University of Toronto and director of the cancer stem cells program at the Ontario Institute for Cancer Research
• Public Service Award: Dr. George Daley, dean of Harvard Medical School and a professor at Boston Children’s Hospital and the Dana-Farber Cancer Institute.

The McEwen Award for Innovation, supported by the McEwen Centre for Regenerative Medicine, recognizes original thinking and groundbreaking research pertaining to stem cells or regenerative medicine that opens new avenues of exploration toward the understanding or treatment of human disease or affliction. Fuchs’ research, ISSCR says, has transformed the understanding of skin stem cells and their application to regenerative medicine, genetic syndromes and cancers.

She has developed many innovative approaches to analyze skin stem cells and their niches, and to dissect the complex controls that orchestrate how stem cells make and repair tissues and what goes awry in genetic conditions and malignancies. “Fuchs has made extraordinary contributions to skin stem cell research throughout her career,” said ISSCR President Sally Temple. “Her work continues to provide new and important insights into all facets of skin and stem cell biology, and the advances she has made extend to the broader scientific and medical community.” Fuchs will present her research in Plenary VI, Tissue Regeneration and Homeostasis, on June 17.

The ISSCR Dr. Susan Lim Outstanding Young Investigator Award recognizes exceptional achievements by an ISSCR member and investigator in the early part of their independent career in stem cell research. The 2017 recipient, Rajagopal, has established a plethora of poster displays and presentations, there will be nearly 200 exhibitors in the exhibit hall ranging from industry to academia.

“We recognize that the translational aspect of stem cell research is vitally important, and it’s a strong aspect of the scientific programming throughout the meeting,” Temple tells DDNews. “This year we’re offering two pre-meeting educational sessions specifically designed for scientists and physicians interested in learning about how stem cell therapies are developed and moved into the clinic.”

“The Workshop on Clinical Translation and the Clinical Advances in Stem Cell Research program both focus on research that is entering the clinic,” she adds. “This year we highlight new approaches to neurodegenerative, eye disease and immunology, and speakers will address the opportunities and challenges that may arise. The goal for us is to make the transition from the lab to the clinic as seamless as possible, prioritizing sound scientific rationale, robust preclinical evidence of safety and efficacy and patient welfare.” She also highlights a focus session on June 13, developed by the ISSCR Industry Committee, called “From the Bench to the Clinic: How to Manufacture Your Cell Product.”

“My research addresses diseases of aging and understanding how cells change as we age. We’re also interested in trying to learn more about the heterogeneity of cells and how they respond to different stimuli. My aim is to develop new cell-based therapies as well as to improve our understanding of the basic biology of aging.” The 2017 recipient, Rajagopal, has transformed the understanding of skin stem cells and their application to regenerative medicine, genetic syndromes and cancers.

He has developed many innovative approaches to analyze skin stem cells and their niches, and to dissect the complex controls that orchestrate how stem cells make and repair tissues and what goes awry in genetic conditions and malignancies. “Fuchs has made extraordinary contributions to skin stem cell research throughout her career,” said ISSCR President Sally Temple. “Her work continues to provide new and important insights into all facets of skin and stem cell biology, and the advances she has made extend to the broader scientific and medical community.” Fuchs will present her research in Plenary VI, Tissue Regeneration and Homeostasis, on June 17.

The ISSCR Dr. Susan Lim Outstanding Young Investigator Award recognizes exceptional achievements by an ISSCR member and investigator in the early part of their independent career in stem cell research. The 2017 recipient, Rajagopal, has established a plethora of poster displays and presentations, there will be nearly 200 exhibitors in the exhibit hall ranging from industry to academia.

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Dr. Sally Temple, president of ISSCR
FUTURE MEETINGS

I N JUNE 2016, the ISSCR announced Los Angeles as the site of the 2019 annual meeting—this will mark the first time the organization will be meeting in that city. It will take place at the Los Angeles Convention Center from June 26–29, 2019.

“Los Angeles offers a rich scientific and cultural backdrop for the ISSCR’s 2019 meeting and we were delighted by the enthusiasm we received from local government, the biotech industry and the scientific and health communities,” said ISSCR CEO Nancy Witty. “We are excited to have USC Stem Cell’s world-class home as our co-sponsor.”

A leader in promoting scientific advances, USC Stem Cell is a collaborative initiative that brings together nearly 100 researchers and clinicians from across the University of Southern California (USC) to translate the potential of stem cell research to the clinic. The initiative is supported by Hong Kong-based businessman and philanthropist Kin-Chung Choi, who extended his “thanks to USC for giving me this rare opportunity to support stem cell researchers from all over the world.”

Dr. Devesh Varma, who was then interim dean of the Keck School of Medicine of USC and director of the USC Roski Eye Institute—he has since been named dean officially—underscored how the conference will benefit not only stem cell researchers, but also the patients they will ultimately serve.

“We are honored to welcome the international community of leading stem cell researchers to the 2019 ISSCR Conference in Los Angeles,” he said. “By bringing together these exceptional scientific minds, the conference will serve as an incubator for new ideas and research collaborations, which will eventually translate into better, more creative therapies for patients.”

In addition to being the home of USC, Los Angeles and the surrounding area is the location of several other major research universities, institutions, academic medical centers and hospitals, including: the California Institute of Technology; Cedars-Sinai Medical Center; Children’s Hospital Los Angeles; City of Hope; University of California, Irvine; University of California, Los Angeles; University of California, Riverside; and University of California, Santa Barbara.

In November 2015, the ISSCR had officially announced the site of next year’s annual meeting, which will be Melbourne, Australia. This will be ISSCR’s first visit to Australia since 2007, when meeting attendees gathered in Cairns.

“The Australians, led by the ASSCR, submitted a strong proposal, uniting local government, industry and the scientific and health communities to paint a picture of the vibrant professional and cultural opportunities the city has to offer,” Witty said. “We were impressed by their unity, enthusiasm and the comprehensive nature of their proposal.”

“Australia has a long history of pioneering and diverse stem cell research and is the home of many groundbreaking discoveries and innovative companies... world-class scientists... are involved in important collaborations all over the globe and are expected to draw participation from their peers in China, Europe, the United States and beyond.”

AWARDS

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Lished himself as a young leader in the field of lung stem cells and lung repair, working with both mouse and human models. As a physician-scientist, Rajagopal has done genetic studies and lineage tracing in the mouse lung, and established a strong research program focused on the repair and regeneration of human lung tissue. His research has provided new insights into the progression of diseases such as asthma, cystic fibrosis, chronic obstructive pulmonary disease and lung cancers.

“Rajagopal and his lab have already made important contributions to the understanding of cell biology in the lung, which have implications for treatment of lung cancer and respiratory disease,” said ISSCR CEO Nancy Witty. “He is also known for his support of young investigators and physician-scientists, which is a great testament to Rajagopal’s commitment to the field. We look forward to involving him in ISSCR leadership in the future.”

Like Fuchs, Rajagopal will present his research in Plenary VI, Tissue Regeneration and Homeostasis, on June 17.

The ISSCR Tobias Award Lecture, started in 2006, is supported by the Tobias Foundation and recognizes original and promising basic hematology research and direct translational or clinical research related to cell therapy in hematological disorders. The winner presents the Tobias Lecture at the ISSCR Annual Meeting.

Award winner Dick has been a leader in the areas of normal stem cell and cancer stem cell biology over the last 30 years, and his discoveries have led to significant advances in cancer biology that have opened new areas of inquiry. By isolating human hematopoietic stem cells, Dick was able to study cellular and molecular mechanisms that regulate their function, and his method is now widely used by researchers around the world. Notably, Dick achieved a breakthrough finding that there are intrinsic differences in tumorigenic potential among cancer cells from the same tumor, and he expanded his work to include common solid cancers.

“Dick has had a tremendous impact on the field of cancer research,” said Temple. “Through his intellectual leadership, his high standard of scientific inquiry and creative insight, he has generated discoveries and approaches that have forever changed the way that researchers approach the development of cancer treatments.”

Dick will present his research in Plenary IV, Chromatin and RNA Biology, on June 16.

The ISSCR Public Service Award is given in recognition of outstanding contributions of public service to the fields of stem cell research and regenerative medicine.

A physician-scientist and leading public advocate for the responsible ethical oversight of human stem cell research, Daley has long been involved in promoting and upholding rigorous standards for the field. He initiated and played key roles in the formulation of three sets of ISSCR guidelines, for the Conduct of Human Embryonic Stem Cell Research (2006), the Clinical Translation of Stem Cells (2008) and Stem Cell Research and Clinical Translation (2016), which are in use around the world.

“Daley’s unwavering commitment to the ethical conduct of research and the integrity of the field is unparalleled,” said Temple. “He continues to advocate on policy issues affecting the field, and is widely respected for his insights, experiences and accomplishments.”

Daley will present in Plenary Session III, Stem Cells and Cancer, June 15.
Hello, hyperpolarized helium MRI

New imaging technique could aid in the development of improved therapies for CF

BY ILENE SCHNEIDER
COLUMBIA, Mo. — According to the Cystic Fibrosis Foundation, more than 30,000 Americans are living with cystic fibrosis (CF), which has no cure. While a drug approved by the U.S. Food and Drug Administration treats the underlying cause of the disease, its effectiveness for each individual is unknown. Researchers from the University of Missouri School of Medicine, who have developed an imaging technique using a specific form of helium to measure a drug’s effectiveness, hope their findings might lead to improved therapies for CF and other lung conditions.

“People with cystic fibrosis have an imbalance of salt in their bodies caused by the defective CFTR protein,” said Dr. Talissa Altes, chair of the Department of Radiology at the medical school and lead author of the study. “The drug ivacaftor targets this defective protein, but to what extent it is successful is not well understood. Our study sought to use a new way of imaging the lung to understand how well the drug is working in patients with a specific gene mutation known as G551D-CFTR.”

The study, “Use of Hyperpolarized Helium-3 MRI to Assess Response to Ivacaftor Treatment in Patients with Cystic Fibrosis,” was published in the Journal of Cystic Fibrosis. The research was supported by Vertex Pharmaceuticals Inc., the manufacturer of ivacaftor, as well as by the Hartwell Foundation and Siemens Healthcare.

HELIXUM CONTINUED ON PAGE 33

Loxo and Ventana set sights on CDx

The companies will collaborate to develop and commercialize a pan-TRK IHC test for larotrectinib

BY KELSEY KAUSTINEN
STAMFORD, Conn. — Biopharmaceutical company Loxo Oncology Inc., which is focusing its efforts on developing selective medicines to treat genetically defined cancers, has struck up a collaboration agreement with Ventana Medical Systems Inc., a member of the Roche Group, for the development and commercialization of a pan-TRK immunohistochemistry (IHC) test. The companies will develop this test as a companion diagnostic to help pinpoint patients with different cancers that might benefit from treatment with Loxo-101 (larotrectinib).

“We are excited to partner with Roche, the global leader in developing and commercializing IHC assays for cancer diagnostics. Our initial technology assessment suggests that an IHC pan-TRK assay is feasible, which is exciting since Roche has thousands of Ventana BenchMark instruments installed worldwide,” Dr. Josh Bilenker, CEO of Loxo Oncology, commented in a press release on the deal. “IHC remains a mainstay of the cancer treatment of early-stage cancer. Unnecessary chemotherapy for patients with a specific gene mutation known as G551D-CFTR,” says Dr. Talissa Altes of the University of Missouri.

Genomic Health reveals Oncotype DX breast cancer test data

New evidence highlights significant impact in reducing burden of unnecessary chemotherapy for patients

BY MEL J. YEATES
GENEVA—Genomic Health recently announced the presentation of 15 abstracts for the Oncotype DX breast cancer test at the 15th St. Gallen International Breast Cancer Conference (SG-BCC) in Vienna, Austria. The Oncotype DX test uses genomic analysis techniques to uncover the unique footprint of each patient’s tumor, and generates a recurrence score result which predicts the likelihood that the patient’s cancer will return and whether chemotherapy is likely to provide benefit.

According to Genomic Health, “The Oncotype DX breast cancer test is the world’s leading provider of genomic-based diagnostic tests that address both the overtreatment and optimal treatment of early-stage cancer. People with cystic fibrosis have an imbalance of salt in their bodies caused by the defective CFTR protein. The drug ivacaftor targets this defective protein, but to what extent it is successful is not well understood. Our study sought to use a new way of imaging the lung to understand how well the drug is working in patients with a specific gene mutation known as G551D-CFTR,” says Dr. Talissa Altes of the University of Missouri.

CONTINUED ON PAGE 33
As Altes explained, ivacaftor is the first approved drug that corrects the defective protein in CF, a transmembrane chloride channel (CFTR). There are more than 1,500 different mutations of the CF gene. The patients in this study had a particular mutation, G551D. In patients with this mutation, the chloride channel is made, folded and transported to the cell surface but it does not open normally. Ivacaftor is a small molecule that opens the defective chloride channel. Prior to the development of ivacaftor, treatments for CF revolved around preventing and treating infection and improving airway mucus clearance. Ivacaftor is the first approved drug of a new class of drugs: the CFTR potentiators.

“The most commonly used method to assess lung function is spirometry,” Altes said. “With spirometry, patients blow out all of the air from their lungs as hard and fast as they can. The airflow is measured at the mouth and compared with normative values. Spirometry is known to be insensitive to early lung disease and small changes in disease severity. Further, it is effort-dependent. This method is not well suited for pediatric patients, because it requires concentration, controlled breathing and cooperation with the spirometry technician.”

She added, “Hyperpolarized helium-3 MRI (helium MRI) uses an inhaled gaseous contrast agent (helium-3) to image the lung in 3D. Areas of the lung that are well ventilated appear bright and areas that are poorly ventilated appear dark on the helium MR images. By looking at the regional lung ventilation, our hypothesis was that helium MRI would be more sensitive to small changes in disease severity than spirometry, which assesses global airflow at the mouth. All patients who improved with treatment on spirometry also improved on helium MRI. Further, we were able to detect improvement in lung ventilation on helium MRI in patients who had little change in spirometry on treatment. Although our study was too small to prove this hypothesis, it is encouraging.”

According to Altes, patients with CF and G551D mutation have shown improvements in lung function on spirometry in prior studies and improvements in lung ventilation on helium MRI in her study. She did note that “It is too early to know whether this will translate into a longer life expectancy, but the community is hopeful. The expectation is that by treating the underlying molecular issue in CF, treatment with ivacaftor will extend the lives of patients with CF.”

She added that Polarean is about to begin a Phase 3 clinical trial for a similar gaseous contrast agent for MRI, hyperpolarized xenon-129. Similar ventilation abnormalities can be demonstrated with either contrast agent. Xenon-129 is more naturally abundant than helium-3, so it is likely to be used clinically. Helium-3 may be used more in research. “More drugs are under development to treat cystic fibrosis and other lung conditions, and improved imaging techniques are needed to test their effectiveness,” Altes concluded. “The importance of this technique is that it may well be a cost-effective tool to aid in the development of these drugs. However, it also can help patients know which medications may work best for their unique conditions.”
LOXO Oncology recently inked a collaboration agreement to develop and commercialize a companion diagnostic for LOXO’s larotrectinib.

LOXO CONTINUED FROM PAGE 32

LOXO Oncology recently inked a collaboration agreement to develop and commercialize a companion diagnostic for LOXO’s larotrectinib.

pathology workup, due in part to its speed, limited tissue requirements, low cost and established reimbursement paradigms. Diagnostics are a crucial part of our commercial strategy, and we believe IHC will be an important tool, alongside next-generation sequencing, that pathologists can employ in screening for patients who may benefit from larotrectinib.

Under the terms of the agreement, Loxo and Roche will use an investigational assay piloted by Loxo Oncology, which will be further developed by Roche via its OptiView DAB detection technology. The companies will work to optimize and validate the assay, and intend to globally commercialize an analytical assay before developing a Class III assay for premarket approval from the U.S. Food and Drug Administration (FDA). Though no financial details were disclosed, the agreement stipulates that Roche will be responsible for developing, obtaining and maintaining regulatory approvals for the companion diagnostic test in the United States, specific countries in the European Union and other countries that recognize the CE mark as a diagnostic registration process.

Larotrectinib is a potent, oral, selective investigational new drug being developed to treat cancers with abnormalities involving the tropomyosin receptor kinases (TRKs). Recent research seems to imply that the NTRK genes that encode for TRKs can become fused to other genes, which leads to growth signals that can result in cancer. An ongoing Phase 1 trial has seen larotrectinib show promising preliminary efficacy, and the drug candidate has received Breakthrough Therapy Designation and Rare Pediatric Disease Designation from the FDA.

Larotrectinib demonstrated preliminary evidence of antitumor activity in all described cases, all of which had progressed following previous treatment.

The same week, the company also announced that oral presentations on larotrectinib had been accepted for the American Society of Clinical Oncology meeting being held in June. Loxo Oncology will share interim clinical data across the RECIST-evaluable TRK fusion clinical trial database from all three of its clinical trials currently under way in a presentation titled “The efficacy of larotrectinib (LOXO-101), a selective pan-TRK inhibitor, in NTRK fusion-positive recurrent glioblastoma.” The studies included cases of three glioblastoma patients, one of whom was treated under an expanded access protocol and two who were treated in the company’s ongoing Phase 2 NAVIGATE trial. Larotrectinib demonstrated preliminary evidence of antitumor activity in all described cases, all of which had progressed following previous treatment.

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At the same meeting, the company will also debut interim pediatric Phase 1 clinical trial data, which is part of the previously mentioned data, in the separate oral presentation “A pediatric phase 1 study of larotrectinib, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family.”

Genomic Health recently shared Oncotype DX breast cancer test data that shows a significant impact in reducing unnecessary chemotherapy for patients.

The data presented at SG-BCC included a pooled analysis of eight international studies including over 2,500 patients, which assessed the impact of the Oncotype DX test on treatment decisions in routine clinical practice. The results showed the average net reduction in chemotherapy use following testing was 42 percent. Also shown was a detailed budget impact assessment comparing the genomic tests available in Germany. The analysis identified Oncotype DX as the test associated with the highest reduction in chemotherapy use because it appropriately classifies more patients at low risk than other tests, resulting in potential net savings of €4,001 per patient tested. And a study from France looked at the test utilization in real-life clinical practice in key patient subgroups, including those with high-risk disease by traditional parameters. The results demonstrated that the use of Oncotype DX in France reduced the use of chemotherapy by 35 percent.

“The traditional criteria used for making chemotherapy clinical decisions may result in substantial over-treatment and toxicity, with unnecessary costs for healthcare systems. The decision to initiate a course of chemotherapy should be as informed as possible. From a health service perspective it is costly and resource intensive to ensure the right therapy for the patient can be even greater,” said Prof. Joseph Grigorescu of the Breast Cancer Expert Center, AHPH Tenon Hospital. “The new Oncotype DX test highlights the impact it is having across Europe to drive a step-change in the quality of treatment decisions. These results, based on real-world clinical practice, indicate that molecular testing provides clinically meaningful information in addition to classical pathological parameters for a significant proportion of patients and support its broader use and public reimbursement.”

Every year in Europe, over 450,000 new cases of breast cancer are diagnosed. While chemotherapy is routinely offered, research shows that less than 10 percent of patients with early-stage breast cancer actually benefit from it. “With-out the Breast Recurrence Score test, doctors can only estimate how likely a patient’s cancer is to return by looking at factors such as age, tumor size, tumor grade and lymph node status,” says Genomic Health. “The Breast Recurrence Score test provides individualized information about [the tumor’s] that’s not available from these clinical and pathologic features.”

Several posters were presented at the St. Gallen International Breast Cancer Conference, providing further evidence that Oncotype DX accurately predicts outcomes and has important clinical utility in patients whose breast cancer has spread to their lymph nodes. An analysis based on the Surveillance, Epidemiology and End Results registry program of the National Cancer Institute looked at breast cancer-specific survival (BCSS) in more than 6,700 patients. The results showed that five-year BCSS was excellent in patients with recurrence score results less than 18 and micrometastases, 1-3 positive nodes. Survival worsened with increasing number of lymph nodes involved and higher recurrence score results.

Spain which assessed the impact of the test on treatment decisions in 217 patients found that among the 71 patients with lymph node-negative breast cancer, there was a 72 percent reduction in chemotherapy use. For the group of 146 patients with lymph node-negative disease, the reduction in chemotherapy was 26 percent.

“The momentum for genomic testing is building as healthcare systems across the world recognize its value to patients and society,” commented Dr. Steven Shak, chief scientific officer of Genomic Health. “These latest presentations clearly highlight the impact of Oncotype DX in reducing chemotherapy usage and driving more cost-effective treatment, as well as its value in providing the clinical confidence that their patients will receive the quality care they deserve.”

Spina, A. et al. (2017). Genomic Health recently shared Oncotype DX breast cancer test data that shows a significant impact in reducing unnecessary chemotherapy for patients. DDNews, 34, 43-44.

Genomic Health presented a proof-of-concept clinical data for larotrectinib for all patients with TRK fusion primary central nervous system cancers at the 2017 American Association for Cancer Research meeting in a poster presentation titled “Potential role of larotrectinib (LOXO-101), a selective pan-TRK inhibitor, in NTRK fusion-positive recurrent glioblastoma.” The studied cases included three glioblastoma patients, one of whom was treated under an expanded access protocol and two who were treated in the company’s ongoing Phase 2 NAVIGATE trial. Larotrectinib demonstrated preliminary evidence of antitumor activity in all described cases, all of which had progressed following previous treatment.

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A review of seven international studies, including more than 9,000 patients with node-positive disease, showed these studies consistently identified patients with a low number of positive nodes (1-3) and low 5-year recurrence score results who had good clinical outcomes. And a study from
Cancer experts get ready to blow into the Windy City

World’s largest clinical cancer research meeting to highlight latest advances in patient and survivor care

BY DDNEWS STAFF

STUDIES SPANNING the spectrum of cancer prevention and care, from immunotherapy and precision medicine to survivorship, will be among the highlights of the 53rd Annual Meeting of the American Society of Clinical Oncology (ASCO). Research results will be released in advance of and throughout the annual meeting, taking place June 2-6 in Chicago, which bears the theme this year of “Making a Difference in Cancer Care With You.”

More than 30,000 oncology professionals from around the world are expected to attend. More than 2,150 abstracts were accepted for presentation at the annual meeting, plus more than 2,890 additional abstracts were accepted for online publication. The vast majority of these abstracts will be publicly posted on abstracts.asco.org after May 17.

ASCO wants you to know that if you think the annual meeting doesn’t kick off until Friday afternoon, you should think again. ASCO has created a slate of pre-annual meeting educational programs that take place prior to the official start of the meeting. The programs consist of both seminars and case-based courses that provide in-depth learning opportunities for attendees. Attendees can register for one seminar or case-based course in addition to their annual meeting registration.

As for programming during the show, here’s what’s in store:

• Education Sessions: These offer interdisciplinary or multidisciplinary explorations of focused areas of clinical oncology. ASCO’s Cancer Education Committee determines the topics and format for these sessions that will best serve the educational needs of annual meeting attendees. Particular care is taken to ensure that these sessions address issues including surgical, radiation, and geriatric oncology; symptom management; health services research; international perspectives; and pathology, as appropriate.

• Clinical Problems in Oncology Sessions: These combine the use of case-based panel discussion with interactive keypad technology for audience participation. These sessions are ticketed and require an additional registration fee.

• Meet the Professor Sessions: These enable interactive discussion between attendees and recognized experts in a variety of subspecialty fields. The format is informal with an emphasis on a face-to-face exchange with the expert. These sessions are ticketed and require an additional registration fee.

• Plenary Session: The Plenary Session, which takes place June 4 from 1 p.m. to 4 p.m., includes 15-minute didactic presentations highlighting abstracts of scientific research deemed to have the highest merit and greatest impact on oncology research and practice. Experts in the field will serve as discussants to place research findings into perspective.

• Oral Abstract Sessions: These include didactic presentations of abstracts representing important clinical and translational research findings by topic category. Presenting authors may use PowerPoint slides to accompany their oral presentation. Experts in the field are chosen to provide comprehensive themed discussions of the findings.
Researchers and scientists recognized for significant contributions to cancer care

ALEXANDRIA, Va.—The American Society of Clinical Oncology (ASCO) and the Conquer Cancer Foundation of ASCO (CCF) in March announced the winners of ASCO's Special Awards, the society's highest honors, and the CCF Women Who Conquer Cancer Mentorship Award. ASCO will recognize this year’s awardees at the 2017 annual meeting in Chicago.

“The meaningful contributions from each of this year’s honorees are leading to improvements throughout the cancer care continuum,” said Dr. Julie M. Vose, immediate past president of ASCO and chair of the Special Awards Selection Committee. “These oncology leaders are changing the lives of people with, or at risk for, cancer, and ASCO is proud to honor them with our most prestigious awards.”

David A. Karnofsky Memorial Award and Lecture
First presented in 1970, the David A. Karnofsky Memorial Award and Lecture honors Dr. Karnofsky by recognizing an oncologist who has made outstanding contributions to cancer research, diagnosis and/or treatment. The winner is Dr. Carl H. June, director of the Center for Cellular Immunotherapies at the Perelman School of Medicine and the director of the Parker Institute for Cancer Immunotherapy at the University of Pennsylvania. He maintains a research laboratory that studies various mechanisms of lymphocyte activation related to immune tolerance and adoptive immunotherapy for cancer and chronic infection. In 2011, his research team published findings detailing a new therapy in which patients with refractory and relapsed chronic lymphocytic leukemia were treated with genetically engineered versions of their own T cells.

Gianni Bonadonna Breast Cancer Award and Lecture
First presented in 2007 and named in honor of cancer research pioneer Gianni Bonadonna, this award recognizes an active clinical and/or translational researcher with a distinguished record of accomplishments in advancing the field of breast cancer and with exceptional mentoring abilities. It goes this year to Dr. Eric P. Winer, who has devoted his professional career to breast cancer research and as a treatment of individuals with breast cancer. He is a professor of medicine at Harvard Medical School and holds several appointments at Dana-Farber Cancer Institute.

Science of Oncology Award and Lecture
Created in 2005, the Science of Oncology Award and Lecture is presented annually in recognition of a recipient’s outstanding contributions to basic or translational research in cancer. Honoreed this year is Dr. Brian J. Druker, director of the Knight Cancer Institute at Oregon Health & Science University, JELD-WEN Chair of Leukemia Research and an investigator of the Howard Hughes Medical Institute. Druker’s work helped pioneer the practice of precision, or personalized, cancer medicine by performing preclinical studies and leading clinical trials that were instrumental to the development of imatinib, a drug that targets the molecular defect in chronic myeloid leukemia.

Allen S. Lichter Visionary Leader Award and Lecture
Created in 2016, this award recognizes a recipient who has drastically changed the oncology field or who has made significant contributions to advance the mission of ASCO, CancerLinQ LLC or the Conquer Cancer Foundation through the honoree’s ability to lead and inspire. The recognition goes to Dr. Patrick J. Loehrer, recognized as a prolific clinical researcher and specialist in the treatment of a variety of cancers including testis, bladder, colon, pancreas and, most notably, thymic.

Pediatric Oncology Award and Lecture
First presented in 2002, the Pediatric Oncology Award recognizes the career achievements of an individual who has contributed outstanding scientific work—laboratory, clinical, or epidemiological—of major importance to the field of pediatric oncology. It goes to Dr. Michael P. Link, a pediatric hematologist/oncologist and the Lydia J. Lee Professor in Pediatric Oncology at the Stanford University School of Medicine. His research interests include the biology and treatment of non-Hodgkin lymphomas and Hodgkin disease, as well as neuroendocrine tumors, psychological management of bone and soft tissue sarcomas in children.

ASCO-American Cancer Society Award and Lecture
First presented in 1993, the ASCO-ACS Award and Lecture recognizes significant contributions to cancer prevention and control research or practice, and the honoree this year is Dr. Dean E. Birenz, the Kutsche Family Memorial Professor of Radiation Oncology and professor of radiology at the University of Michigan. His scientific career has been devoted to translational research in cancer therapeutics with a focus on the development of immunotherapies, reprogramming of tumor cells to reduce tumor-promoting qualities and improving outcomes for patients.

B.J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology
Created in 2005, this award recognizes an ASCO member who has made outstanding contributions to the research, diagnosis and treatment of cancer in the elderly. This year it goes to Dr. David L. Drotz, who has dedicated his work to the integration of geriatric assessment in decision making for treating older people with cancer.

Distinguished Achievement Award
Created in 2009, this award recognizes a person involved in patient advocacy activities that have an impact on public awareness of cancer, its causes, cures or treatments, or activities that result in additional support either legislatively or fiscally for cancer research, treatment, prevention or care. This year it goes to Dr. Susan L. Weiner, founder and director of The Children’s Cause for Cancer Advocacy.

Humanitarian Award
First presented in 2011, the Humanitarian Award recognizes an oncologist who personifies ASCO’s mission and values going above and beyond the call of duty in providing outstanding patient care through innovative means or exceptional service or leadership. It goes to Olufumilayo O. Olopade, a medical oncologist and international renowned expert in breast cancer, who serves as Walter L. Palmer Distinguished Service Professor of Medicine and director of the Center for Innovation in Global Health at The University of Chicago.

Women Who Conquer Cancer Mentorship Award
First presented in 2016, this honor recognizes a person involved in patient advocacy activities that have an impact on public awareness of cancer, its causes, cures or treatments, or activities that result in additional support either legislatively or fiscally for cancer research, treatment, prevention or care. This year it goes to Dr. Susan L. Weiner, founder and director of The Children’s Cause for Cancer Advocacy.

ASCO continued from page 35
- from predeterminated abstracts.

- Clinical Science Symposium: This provides a forum for science in oncology, providing foundational education on a specific topic with the presentation of abstracts. Experts in the field place studies in the appropriate context based on the strength of the evidence and critically discuss the conclusions in terms of their applicability to clinical practice.

- Highlights of the Day Sessions: With this offering, ASCO invites expert discussants to present key findings, put abstracts into clinical context and provide an overview of the previous day’s oral abstract sessions.

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

Plenty of vitality in vaccines

INC Research, which provides clinical trial services for Phases 1 to 4, has been busy lately with plenty of work in the vaccines arena.

An April acquisition in TNAs

LGC snaps up Axolabs, boosts manufacturing capacity for therapeutic nucleic acids

LGC’s latest acquisition is of Axolabs, which is part of an effort to bolster its capacity as a leading solutions provider for therapeutic nucleic acids.

BRIEFS

ProTrials adds data management services

SAN JOSE, Calif.—ProTrials Research Inc. recently announced the expansion of its service offerings, and will now also provide data management services and a range of electronic data capture (EDC) platforms. The company boasts capabilities across the clinical trial spectrum, including in disease areas such as oncology, ophthalmology and infectious disease. Also in the first quarter, ProTrials attended this year’s Outsourcing in Clinical Trials, West Coast conference.

“With ProTrials, we are committed to advancing the quality of clinical trials,” said Jodi Andrews, co-founder and co-CEO of ProTrials. “We are pleased to work toward a full-service offering by providing our clients with data management and EDC services, both of which support our efforts toward providing full-service capabilities to our clients.”

SYMBIOSIS expands across the pond

STIRLING, U.K.—SYMBIOSIS Pharmaceutical Services has announced that it will be opening an office in Cambridge, Mass., a commercial site that will support the contract management organization’s East and West Coast clients. The company has seen revenues grow by 40 percent in the last 12 months, and has increased its staff by 30 percent to meet service demand.

Colin MacKay, CEO at SYMBIOSIS, commented: “Given Cambridge is the epicenter of the global biotech community, it is the ideal location for us to open an office in the U.S. Back in 2015, we took the decision to strategically focus on the North American market after we identified a surge in funding for early-stage biotech companies … Since strengthening our U.S.-focused personnel and developing our relationships with networks like ISPE and MassBio, we have significantly grown our U.S. client base, which is projected to account for around half of our revenues in 2017. Opening the office on the U.S. East Coast is the next stage of the company’s growth strategy.”

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Picking up the pace

PPD advances on a trio of fronts: rare disease, nephrology and HIV

BY H. NATHANIEL KOONCE
WILMINGTON, N.C.—In the early months of this year, contract research organization Pharmaceutical Product Development LLC (PPD) has made several moves to expand relationships or services in areas as disparate as rare diseases, renal disease and HIV/AIDS.

On Feb. 28, Rare Disease Day, the company announced that it had established a Rare Disease and Pediatric Center of Excellence as a clearinghouse for all its rare disease and pediatric-related drug development activities.

“Our new center of excellence builds on PPD’s longstanding experience in the area of rare diseases, offering our clients a solution to address the special drug development considerations of rare diseases and pediatrics,” Dr. Karen Kaucic, PPD senior vice president and head of the center of excellence, said in a media release.

In the past five years, PPD has conducted more than 220 studies with more than 50,000 patients, and conducted more than 400 clinical trials, enrolling more than 97,000 patients across a wide range of therapeutic indications, including infectious diseases, respiratory, cardiology, oncology and immunology.

The new center will leverage the experience of Kaucic and her team of pharmaceutical and clinical research professionals in rare disease trial design and execution in such disciplines as product development, clinical operations, commercial strategy and early engagement. The team will work to address the specific challenges presented by populations of rare disease and pediatric patients, with support for end-to-end clinical trial solutions in such areas as feasibility strategy, clinical information, biostatistics, pharmacovigilance, lab operations and business analytics.

PPD also intends to use its pediatric investigator network to provide clients with faster trial startup, more predictable patient enrollment and higher-quality data. It will employ a framework built specifically for this center to ensure the application of best practices and develop a customized approach to address the unique needs of these trials.

“With a great majority of rare diseases touching children,” said Kaucic, “we believe our approach will enable us to be a more connected and active partner. Our clients can depend on us for the latest trial design innovations, the ability to navigate complex trial logistics and our keen understanding of the needs of customized patient access in low-prevalence, widely dispersed patient populations.”

From diseases that touch only a few, to ones that touch very many, PPD has made a significant addition to its services in the area of kidney diseases, announcing in February that it has entered into a collaboration with Frenova Renal Research, a leading drug and medical device clinical development services provider dedicated exclusively to renal research.

PPD stands to benefit from this arrangement in two ways. First, Frenova offers an enormous cache of data and expertise to PPD and its clients. As part of kidney care and services company Fresenius Medical Care North America (FMCNA), which hosts a network of more than 2,200 dialysis centers nationwide, Frenova maintains a network of resources encompassing 260 research sites with 450 principal investigators and access to more than 135,000 active end-stage renal disease patients and 350,000 active patients with chronic kidney disease. FMCNA itself has collected data on more than 1 million patients, including data on more than 250 million dialysis treatments, more than 1 billion lab tests, more than 1 billion laboratory results.

“The opportunity to collaborate with Frenova enhances our ability to connect our clients with researchers recognized as world leaders in the field of nephrology and further strengthens our industry-leading global site and patient capabilities by helping to deliver seamless access to patients, sites and data sources,” said Ulrich Zoeller, vice president of project management and general medicine PPD intends to use its pediatric investigator network to provide clients with faster trial startup, more predictable patient enrollment and higher-quality data in the area of rare diseases.

“Picking up the pace...” CONTINUED ON PAGE 39

INC CONTINUED FROM PAGE 37

since 2011, in diseases such as Ebola, Zika, meningitis, rotavirus, smallpox and influenza, among others. In that time, INC Research reports it has delivered all vaccine clinical trials on time or ahead of schedule.

“We have seen a steady flow of requests for support in continuing the development of flu vaccines over the past few years,” Anderson tells DDNews of the disease focus INC has seen lately in the vaccine field. “However, we’re seeing more interest and inquiries from companies that are on the path for developing universal flu vaccines, addressing the need for a flu vaccine that protects against future seasonal and pandemic strains and then outbreaks of diseases like Ebola and Zika that are known in the media. We have seen more urgent requests and a lot of developers launching into that space quickly. What we’ve seen is an increase in funding for vaccine development, coming both from the government side and from the commercial side; I think the vaccine industry has grown quite a bit, and I do not see it slowing down anytime in the near future.”

A good deal of INC’s work in vaccines has centered on launching and expanding its Vaccine Catalyst Site Network. This effort, launched in 2016, consists of an integrated team of experienced sites in the United States, and aims to benefit all stakeholders in vaccine research with the goal of maximizing both sponsor choice for patients participating in vaccine clinical trials as well as aligning with protocols for vaccine investigative sites. All participating sites have been identified as high-performing in the field of vaccine research and work closely with INC and each other to deliver vaccine studies more rapidly.

“The Vaccine Catalyst Site Network is a whole infrastructure, or ecosystem really, if you want to call it that; it’s more than just CRO-to-site relationships,” Anderson explains. “We’re building an infrastructure to be able to deliver efficiently and innovatively in the clinical trial space for vaccines, where it includes our vendors and our other functional areas so that we can deliver on a 30-day start from final protocol. We have seen increasing interest to find out more about what’s possible and what the Vaccine Catalyst Site Network can offer, and we’re excited about the future of it as it continues to evolve.”

INC Research has also been expanding its staff, having recently announced four new additions to its Real-World & Late Phase (RWLP) and Global Consulting offerings. The RWLP team focuses on real-world, evidence-based data collection, and collaborates with the Global Consulting business to support customers at all stages of development. The new appointments include Dr. James Featherstone, senior vice president of strategy consulting; Janet Baldwin, vice president of RWLP; head of North America operations; Nathalie Doize, vice president of RWLP, head of Europe and Asia/Pacific operations; and Alastair MacDon ald, executive director of RWLP.

Picking up the pace...” CONTINUED ON PAGE 39

“...I think the vaccine industry has grown...”
Cream of the CRO crop

PSI CRO, INC Research, Chiltern among top CROs rated by investigative sites globally in new CenterWatch survey

BY DDNEWS STAFF

BOSTON—More than 1,300 global investigative sites across 15 countries rate the best contract research organizations (CROs) with which to work in a new survey conducted by CenterWatch, a leading publisher and provider of global clinical trials information. The survey results were released April 3 for The CenterWatch Monthly publication.

Investigative sites rated CROs on more than three dozen individual relationship attributes in six categories. The seven highest-rated companies were PSI CRO, INC Research, Chiltern, QuintilesIMS, Parexel, Icon and PPD.

The results reflect how CROs have adopted a more strategic view of site relationships in recent years and invested resources in a wide range of initiatives designed to ease the site burdens, support study conduct and improve the efficiency of clinical development processes. For the first time, investigative sites report their working relationships have become more effective and overall CRO performance matches that of sponsor companies.

Though there were significant improvements in site-CRO relationships, areas identified in the survey in need of improving include providing knowledgeable, well-trained clinical research associates, being organized and having easily accessible staff.

“The gaps are closing between sponsors, CROs and sites, resulting in stronger working business relationships that are necessary to ensure clinical trials are conducted efficiently, effectively and ethically,” said Joan Chambers, chief operating officer of CenterWatch. “Each partner recognizes the importance of working together. New initiatives are being implemented and resources added to ensure goals are met. While the survey revealed significant improvements, I believe we will start to see initiatives formulated to address lingering problem areas. As the industry continues to evolve, we will see a continued focus on building stronger relationships between sponsors, CROs, sites and the new partner—patients.”

The CenterWatch Global Investigative Site Relationship Survey was first launched in 1997. This year’s survey was conducted online from October 2016 to January 2017, and asked principal investigators, sub-investigators and study coordinators to rate the sponsors with whom they worked during the past two years on 37 relationship attributes, from study planning to innovation, and to rate the importance of those attributes as well. Key changes to the survey included new attributes that addressed issues related to patient-centric protocol design and risk-based monitoring. A total of 12 CROs with sufficient sample sizes were profiled in the analysis.

LGC

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lar research, in-vitro diagnostics, therapeutic and other applied sciences. They are the critical components for consequential investigations such as human and veterinary diagnostics, pathogen and microbe detection, environmental screening, epidemiological surveillance and agricultural selection.

Based in Kulmbach, Germany, Axolabs employs 60 people and delivers integrated research solutions for TNAs, covering in-silico design, synthesis, analytics, bioanalyt- ics, biology, pharmacology and consulting services. Axolabs’ expertise spans a wide range of TNA modalities, including anti- sense oligos, siRNAs, immunomodulatory oligos, aptamers, microRNAs and microR- NA mimics, synthetic mRNAs and guide RNAs for CRISPR applications. Axolabs’ management team will remain with the business following the transaction.

“It is clear that LGC shares our passion for delivering the highest-quality science and service for our customers,” commented Dr. Hans-Peter Vorbroicher, managing director of research for Axolabs. “Combining Axolabs’ preclinical expertise and LGC’s GMP manufacturing capabilities allows us to support our clients further along the drug development pathway. Moreover, the access to LGC’s leading science and international reach enables us offer a broader set of solutions for our customers.”

In conjunction with the acquisition of Axolabs, LGC also announced a major investment at its Biosearch subsidiary in Petaluma, Calif., to expand its GMP oligonucleotide manufacturing capacity to provide TNA synthesis to the 1-kg scale in support of early-stage clinical trials. Acquired in 2015, Biosearch specializes in the genomics and life-sciences industries for the design, development and manufacture of custom oligos and associated reagents for the medical diagnostics, research and applied markets. Biosearch’s

“With more than 16 years’ experience in the therapeutic nucleic acid market, Axolabs enjoys a strong reputation for scientific excellence, quality and reliability—attributes that match LGC’s. Axolabs’ in-depth know-how in the TNA drug development field complements LGC’s capabilities in GMP oligo manufacture, CMC analytical and bioanalytical services.”

Dr. David Griffiths, managing director of LGC’s LMS division

products enable the amplification, detection and quantification of DNA molecules.

In addition, LGC acquired Prime Synthesis Inc. (PSI), a leading producer of controlled pore glass (CPG) supports for oligonucleotide synthesis. Complementing LGC’s existing genomics offering, PSI’s products are supplied to the pharma and biopharma, academic research, contract manufacturing, medical diagnostics and biochemical reagents markets.

The combination of the PSI business with the Biosearch capacity provides increased supply chain resiliency for LGC clients based on the manufacturing footprint in both the United States and Europe. It also provides a platform for scale up of CPG production, which aids those customers conducting late-stage clinical trials with oligo therapeutic candidates.

PPD

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recruitment. Fifteen of Frenova’s 260 research sites are proprietary FiRST Up sites, which use coordinated research processes that enable faster site startup and streamlined study execution.

The effectiveness of PPD’s services, and the longevity of their relationships, is evidenced by a third announcement, made in March, that its long-standing contract with the Division of AIDS of the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH), has been renewed for the fifth time. This contract was first implemented in 1990, and the renewal carries the relationship forward to 2024.

As part of the contract, PPD will continue to predict risks to clinical trial participant safety and data integrity based on measures of site performance and other known risk factors. The renewed contract covers support for a broad scope of research related to HIV or HIV co-infections that includes monitoring therapeutic trials, prevention trials and vaccines work.

“The extension of this contract will allow PPD to provide important comprehensive clinical site and study monitoring services to the NIH in some of the most pivotal and exciting directions in AIDS research,” commented William Sharbaugh, chief operating officer of PPD. “We are privileged to continue our collaborative relationship with the NIH, leveraging our considerable resources as one of the world’s largest CROs, while capitalizing on our in-depth knowledge of infectious diseases.”

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

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**BRIEFS**

**AMPAC adds space, capabilities**

**RANCHO CORDOVA, Calif.**—The AMPAC Analytical business unit of AMPAC Fine Chemicals LLC has quadrupled its analytical services capacity, the company reported recently, having added 13,000 square feet of lab space at a new facility in El Dorado Hills, Calif., and enhancing specialized analytical testing abilities to support existing and forecast FDA requirements. The unit’s offerings include inductively coupled plasma mass spectrometry and inductively coupled plasma optical emission spectrometry techniques, as well as X-ray powder diffraction, particle size distribution, and dissolution of drug product.

“The market for U.S.-based pharmaceutical manufacturing and services continues to expand. We are rapidly increasing our depth and breadth of capacities and capabilities to remain at the forefront of the pharmaceutical fine chemical industry,” said Dr. Aasim Malik, CEO of AMPAC Fine Chemicals.

**CBMG expansion to boost clinical trial capacity**

**SHANGHAI, China & CUPERTINO, Calif.**—Cellular Bio-medicine Group Inc. (CBMG) has completed its newly expanded 30,000-square-foot facility in Huishan High Tech Park in Wui, China. An expected 20,000 square feet of the WuLi GMP facility will be used for advanced stem cell culturing, centralized plasmid and viral vector production, cell banking, and reagent development. The company believes that this facility, together with its Zhangjiang Shanghai and Beijing GMP facilities, will be able to support simultaneous clinical trials for five different CAR-T and stem cell products, or have the capacity to treat up to 10,000 cancer and 10,000 knee osteoarthritis patients annually.

Tony (Bizuo) Liu, CEO of CBMG, remarked that “We will now be able to centralize, standardize, and automate our manufacturing capabilities fully in-house while enhancing our capacity to meet the production demands of multiple products in development as part of our overall chemistry, manufacturing and controls process.”

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**Doubling down on KRAS**

Boehringer Ingelheim and Vanderbilt University expand collaboration to tackle difficult-to-treat cancers

**BY JEFFREY BOULEY**

INGELHEIM, Germany—In an effort to expand its long-term partnerships with academic leaders in the oncology field and further boost its KRAS research and development efforts, Boehringer Ingelheim (BI) earlier this spring announced a new collaboration with U.S. academic institution Vanderbilt University in Nashville, Tenn. The multiyear program complements an existing collaboration between the pharma and the university by focusing on the research and development of small-molecule compounds targeting the protein SOS (Son Of Sevenless). This molecule activates KRAS, a molecular switch that is considered to play a key role in the onset of many of the deadliest cancers.

BI had established the original Vanderbilt collaboration in 2015 with the cancer drug discovery laboratory of Dr. Stephen W. Fesik, the Orrin H. Ingram II Chair in Cancer Research and a professor of biochemistry, pharmacology and chemistry. The aim of that collaboration was to pursue the research and development of small-molecule inhibitors of oncogenic Ras for the treatment of cancer. That work achieved two major milestones by identifying lead compounds that bind to KRAS with high affinities, which could lead to developing novel cancer treatments that work on KRAS, “says Dr. Lawrence J. Marnett, the Mary Geddes Stahlman professor of cancer research and dean of basic sciences for the Vanderbilt University School of Medicine.

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**The chicken or the egg**

New study finds high prescription drug costs are not driving up U.S. healthcare costs

**BY DDNEWS STAFF**

SAN FRANCISCO—According to a new report released today by the Pacific Research Institute, a free-market think tank, there might be a question of “Which came first, the chicken or the egg?” when it comes to prescription drug costs and their effect on increasing healthcare costs. In PRI’s view, a more realistic evaluation of U.S. prescription drug prices is that high drug prices are not actually driving up healthcare costs overall, but rather reflect the higher U.S. healthcare costs compared to the rest of the world.

“It’s a common misconception that expensive prescription drug costs are driving up America’s healthcare costs overall,” said Dr. Wayne Winegard, PRI senior fellow in business and economics, and the study’s author. “Our new study finds that...”

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**On the cutting edge**

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

**BY JEFFREY BOULEY**

ATE MARCH saw Dolomite Bio, a brand of Blacktrace Holdings Ltd., celebrate the first anniversary of its launch, marking the end of what it calls “a fruitful year in business.” This biology-focused brand, a spinout from sister company Dolomite Microfluidics, is dedicated to the development of innovative products for high-throughput single cell encapsulation.
KRAS

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therapeutics based on molecules that are able to block this critical cancer driver.

“With new technologies and the scientific discoveries made by Prof. Fesik’s laboratory, we believe the time is now right to step up research efforts to develop novel cancer treatments that work by attacking KRAS and associated signaling pathways,” said Dr. Clive R. Wood, senior corporate vice president of discovery research at BI.

“Prof. Fesik is a pioneer in the discovery of small molecules that bind to and inhibit challenging drug target proteins. His partnership with Boehringer Ingelheim will expedite efforts to discover novel cancer treatments that work on KRAS,” added Dr. Lawrence J. Marnett, the Mary Geddes Stahlman professor of cancer research and dean of basic sciences for the Vanderbilt University School of Medicine.

Mutations in the genes that encode KRAS contribute to some of the most aggressive and deadly cancers, including up to 25 percent of lung, 35 to 45 percent of colorectal and about 90 percent of pancreatic tumors. KRAS has been a particularly difficult protein to target, and no effective treatments targeting KRAS have been developed since its discovery in human cancers more than 30 years ago, the company notes.

The new collaboration with Vanderbilt University further strengthens Boehringer Ingelheim’s oncology pipeline. Lung cancer—which of course is one of the cancers closely associated with KRAS—is an area in particular where BI, already one of the world’s 20 leading pharma companies, seeks to become an industry leader. “Boehringer Ingelheim has successfully launched two products for NSCLC, which have been approved and established as valuable additions to current clinical practice,” the company notes. “Continuous insights and learnings from research and development are key parts of innovation and our way forward to advance clinical practice in lung cancer and other cancer types.”

And speaking of the lung, other recent news out of BI reveals that the first patient recently was enrolled in the PF-ILD (progressive fibrosing interstitial lung disease) trial. This study investigates the efficacy and safety of nintedanib in a range of progressive fibrosing lung conditions other than idiopathic pulmonary fibrosis (IPF).

More than 200 conditions can affect the tissue and space around the air sacs of the lungs, or the interstitium, and these conditions are called interstitial lung diseases (ILDs). Based on clinical observations, there are groups of patients with ILD who—inde-
For your approval

A collection of recent regulatory approvals and other actions globally

BY JEFFREY BOULEY

ELY MAY saw the U.S. Food and Drug Administration (FDA) expand the approved use of Bayer’s Stivarga (regorafenib) to include treatment of patients with hepatocellular carcinoma (HCC or liver cancer) who have been previously treated with the drug sorafenib, marking the first FDA-approved treatment for a liver cancer in almost a decade.

“Limited treatment options are available for patients with liver cancer, the gr. Dr. David Melson, acting director of the Office of Hematology and Oncology Products in the FDA’s Center for Drug Evaluation and Research and director of the FDA Oncology Center of Excellence. “This is the first time patients with HCC have had an FDA-approved treatment that can be used if their cancer has stopped responding to initial treatment with sorafenib.”

This Stivarga application was granted Priority Review designation as well as Orphan Drug Designation.

PRO 140 deemed too broad to be an orphan drug

VANCOUVER, Wash.—In mid-April, CytoDyn Inc., a biotechnology company focused on the development of new antibody therapies for combating human immunodeficiency virus (HIV) infection, announced that its application for Orphan Drug Designation (ODD) was not granted by the Office of Orphan Products Development of the FDA because PRO 140 appears to have the potential to treat more than the subset of multidrug-resistant HIV patients for which the designation was requested.

CytoDyn is currently conducting a pivotal Phase 2b/3 trial with PRO 140 in combination with other antiretroviral agents in the patient population submitted to the FDA in the ODD application. However, CytoDyn is also conducting a 300-patient Phase 2b/3 trial with PRO 140 as a single-agent maintenance therapy for HIV-infected patients, which is a U.S. patient population that far exceeds the 200,000-patient threshold for ODD.

Tecentriq wins FDA approval for advanced bladder cancer

SOUTH SAN FRANCISCO, Calif.—Genentech, a unit of Swiss drugmaker Roche Holding AG, announced recently approval from the FDA for its already approved immunotherapy drug, Tecentriq, to treat advanced bladder cancer.

Tecentriq, also known as atezolizumab, received the go-ahead under the FDA’s accelerated approval program as a first-line treatment for patients with advanced bladder cancer who are not eligible for standard cisplatin chemotherapy. The drug was earlier approved in patients with advanced or metastatic bladder cancer whose disease worsened within a year of receiving chemotherapy.

The approval, which came six months after the FDA approved Tecentriq for the treatment of non-small cell lung cancer, is a boost to the Swiss drugmaker’s bid to expand indications for the drug. Tecentriq belongs to a closely watched class of drugs called PD-1 inhibitors, which help the immune system fight cancer by blocking a mechanism that tumors use to evade attack.

Regulatory pathway opens for LDL-C-lowering indication for bempedoic acid

ANN ARBOR, Mich.—March saw Esperion Therapeutics Inc., a lipid management company focused on developing and commercializing convenient, complementary, cost-effective, once-daily, oral therapies for the treatment of patients with elevated low-density lipoprotein cholesterol (LDL-C), announce that the FDA recently confirmed that Esperion’s LDL-C-lowering program is adequate to support approval of an LDL-C-lowering indication for bempedoic acid.

Esperion plans to submit a New Drug Application for the first half of 2019 for an LDL-C-lowering indication based on the successful completion of the global pivotal Phase 3 program. The proposed product label would include specific language for use of bempedoic acid as an adjunct to maximally tolerated statin therapy in patients with hypercholesterolemia, specifically those at high cardiovascular disease risk with atherosclerotic cardiovascular disease and/or hereditary familial hypercholesterolemia who require additional LDL-C lowering.

“We are very pleased to have achieved clarity from FDA regarding Esperion’s LDL-C-lowering development program,” said Tim M. Mayleben, president and CEO of Esperion. “Our experienced lipid management team has worked closely with regulatory authorities and our key advisors to achieve this encouraging outcome.”

Marketing authorization granted to Darzalex

COPENHAGEN, Denmark—Genmab A/S announced in early May that the European Commission had granted European Marketing Authorization for Darzalex (daratumumab) in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy,

“The notion is that daratumumab is an antibody that can evade attack.

The FDA clears IND application for UCART19

SERVIER, France—Servier, together with Pfizer Inc. and Cellectis, announced in March that the FDA had granted Servier Investigational New Drug clearance to proceed in the United States with the clinical development of UCART19, an allogeneic, gene-edited cellular therapy candidate to treat relapsed/refractory acute lymphoblastic leukemia.

Servier is sponsoring the CALM Phase 1 study on UCART19. In 2015, Servier acquired exclusive rights from Cellectis for UCART19, which is being co-developed by Servier and Pfizer.

COST CONTINUED FROM PAGE 40

Drug price growth is actually not the primary cause of America’s healthcare affordability problem. This is due to the current healthcare delivery system. Most evaluations, he argues, focus incorrectly on the list prices of the drugs. However, this is a distorted view as these vary significantly from the net prices, or the prices consumers pay following all discounts and negotiated payments.

Among the other key points in the recently titled “U.S. Pharmaceutical Pricing in Context,” are:

• Since 1969, healthcare inflation has outpaced drug price inflation. More recently, drug price inflation has increased, likely driven by hospital drug prices and the increase in new, novel medications. Typically, drug prices rise at a faster rate when there are more innovations.

• Total expenditures on pharmaceuticals relative to overall healthcare expenditures have risen and fallen in an unrelated matter. This reportedly shows that increases in drug prices are not driving increases in healthcare costs.

• An apples-to-apples comparison of U.S. drug prices with those in other countries, adjusted for higher overall medical price inflation, shows that higher U.S. drug prices simply reflect higher overall domestic medical prices.

• The current drug pricing process includes “pervasive incentives” that drive up costs. Reforms to simplify this process would theoretically enable list prices to reflect transaction costs more accurately.

• Pfizer also pointed out in the report that hospitals are reimbursed for the price paid for drugs under Medicare Part B. Reforms to provide reimbursement based on the value of the drug, not the cost, would help drive down costs and increase information available for doctors, pharmacists and patients.
For more information, visit www.DDN-News.com

EDGE
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directed evolution by FACS sorting, functional antibody screening in droplets and cell encapsulation in hydrogels.

“Dolomite Bio was launched to focus on developing novel products for high-throughput single-cell research, taking advantage of Dolomite Microfluidics’ underlying technology and the Blacktrace group’s understanding of the market to serve customers in this rapidly growing field,” said Mark Gilligan, CEO of Blacktrace Holdings. “One year on, we are delighted with the brand’s progress and look forward to further success as we move into the future.”

BioTek opens second solar facility

WINOOSKI, Vt.—BioTek Instruments continues to strengthen its commitment to sustainability by announcing the opening of their second solar facility. In addition to the company’s existing 500-kilowatt solar farm in Whitefield, Vt., a new, 88-kilowatt photovoltaic solar energy farm has been put into action in Milton, Vt.

The additional renewable energy will provide power to BioTek’s new 22,000-square foot facility expansion and is expected to offset 100 percent of the company’s annual electricity costs well into the future.

Transfection technology for primary cells

VANCOUVER, British Columbia—Precision NanoSystems says it is helping scientists “to push the boundaries of neuroscience research” with a range of efficient and easy-to-use primary cell transfection kits. Combining Dolomite Bio’s core technology is open and fully scalable, enabling microdroplet encapsulation of individual cells and molecules from a few to millions in minutes, according to the company.

G-BOX Chemi X26 imager studies effects of stressors on bacteria

CAMBRIDGE, U.K.—Syngene, a manufacturer of image analysis solutions, recently announced that its G-BOX Chemi X26 multi-application imager is being used by scientists at the University of Warwick to rapidly and accurately analyze how gram-positive bacteria react to stressors.

“B. subtilis expresses over 1,500 noncoding RNAs, and we want to determine what they are regulating and how they are doing it. As part of this research we’re using a G-BOX Chemi X26 system to analyze chemiluminescent RNA and proteins, as well as image B. subtilis and E. coli colonies on 25 cm plates to identify interesting clones,” said Dr Emma Denham, assistant professor of molecular bacteriology at the University of Warwick.

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Mark Gilligan, CEO of Blacktrace Holdings

its user-friendly NanoAssemblr microfluidics systems with advanced nanoparticle technology, the company has developed the Neuros, Astrocy and iNeuro9 nonviral gene transfection kits to allow rapid and easy knockdown or expression of genes in primary cells, both in vitro and in vivo.

The company’s transfection kits are optimized for nonviral delivery of short interfering RNA, messenger RNA or plasmid DNA into various neural cell types, such as neurons, astrocytes and induced pluripotent stem cell-derived neurons.

Genedata Screener offers APC functionality and integration with Nanion SyncroPatch 384PE

BASEL, Switzerland & MUNICH, Germany—Earlier this year, Genedata, a provider of advanced software solutions for drug discovery and life-sciences research, announced new automated patch clamp (APC) functionality in Genedata Screener for Ion Channel Screening and a Genedata Ready-To-Run integration with Nanion SyncroPatch 384PE. The package reportedly provides seamless data capture and innovative analysis of Nanion’s multisweep, multidose current traces as well as interactive access to the raw traces for visualization and analysis optimization.

APC technology provides scalable functional measurement of ion channels, which are increasing in complexity and importance in drug discovery and development.

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Blitz F16-83 aims to acquire Epigenomics

BERLIN—Late in April, Epigenomics AG, Cathay Fortune International Co. Ltd. (CFIC) and Blitz F16-83 GmbH (which will in the future be known as Summit Hero Holding GmbH and is a subsidiary of CFIC) entered into a business combination agreement regarding the takeover of Epigenomics by the bidder, Blitz F16-83.

Pursuant to the agreement, the bidder has agreed to launch a voluntary public takeover offer pursuant to the German Takeover Act to acquire all of the outstanding ordinary shares of Epigenomics. The transaction values Epigenomics’ equity, including net cash, at approximately €171 million.

The intention is to maintain the locations of the business operations of Epigenomics and its main business activities at significant locations, including the company’s headquarters in Berlin. The current workforce of Epigenomics is not intended to be reduced as a consequence of the transaction.

In the event the takeover is successful, the plan is also to keep the current members of the executive board in place, with Greg Hamilton as CEO of Epigenomics and Dr. Uwe Staub as chief operating officer.

Epigenomics is a molecular diagnostics company focused on blood-based detection of cancers using its proprietary DNA methylation biomarker technology. The company develops and commercializes diagnostic products across multiple cancer indications with high medical need.

G-BOX Chemi X26 imager studies effects of stressors on bacteria

CAMBRIDGE, U.K.—Syngene, a manufacturer of image analysis solutions, recently announced that its G-BOX Chemi X26 multi-application imager is being used by scientists at the University of Warwick to rapidly and accurately analyze how gram-positive bacteria react to stressors.

“B. subtilis expresses over 1,500 noncoding RNAs, and we want to determine what they are regulating and how they are doing it. As part of this research we’re using a G-BOX Chemi X26 system to analyze chemiluminescent RNA and proteins, as well as image B. subtilis and E. coli colonies on 25 cm plates to identify interesting clones,” said Dr Emma Denham, assistant professor of molecular bacteriology at the University of Warwick.
**New microplate-based method to measure OCR and ECA**

**Irvine Scientific**

PRIME-XV T Cell CDM is the first commercially available chemically-defined, animal component-free medium for T cell culture. The new medium has been developed to maximize consistent growth of T cells while maintaining their functionality and therapeutic potential.

**New Enteroviruses monoclonal antibodies**

**ViroStat Inc.**

Enteroviruses are a diverse group of RNA viruses including Poliovirus, Rhinoviruses, Coxsackie A & B viruses, and Echoviruses. Most are acquired via the fecal-oral route and exhibit symptoms ranging from the common cold and conjunctivitis to myocarditis, sepsis and flaccid paralysis. The most recently discovered members of this genus are named as EV88, EV92, EV97, etc. ViroStat has just released three new specific monoclonal antibodies to EV97 (hand, foot and mouth disease).

**Evaluate the accuracy of pipettes in seconds**

**Next Advance**

Low-cost, fast, and easy to use, the Checkit can save money on calibration services while giving researchers the confidence that their pipettes are delivering accurate volumes. In addition, the ISO 8655 calibration standard applies the same allowable volumetric error throughout a pipette’s range, so the allowable error at the bottom of the range is 20 percent for a 10 uL pipette, and even greater for lower volume models. So, while a pipette may be labeled as calibrated, the pipette check will reveal the actual accuracy of the pipette, within 1 percent. In fact, many pipette manufacturers recommend regular in-laboratory checking of pipettes in addition to good maintenance and scheduled calibration.

**Next Advance**

www.nextadvance.com/pipette-checkit/

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**Enzymatically reversible reagent reservoirs save money and space**

**INTEGRA Biosciences**

INTEGRA offers a range of high-quality multichannel reservoirs that feature reusable bases. This environmentally friendly design allows users to reuse the sturdy base and save money, as you only replace the disposable inserts. INTEGRA reagent reservoirs have been designed to nest inside each other, making it possible to get twice as much reagent in the space of traditional reservoirs, reducing both inventory space requirements and shipping costs. Each INTEGRA reservoir base accommodates two reservoirs with one acting as a lid to allow short-term benchtop storage of reagent while preventing evaporation or contamination from airborne particulates.

**INTEGRA Biosciences Corp.**

www.integra-biosciences.com

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**Cell lines, media for difficult-to-culture tumor types**

**AMSBIO**

AMSBIO has a new range of cancer cell lines and culture media for the most difficult-to-culture tumor types where no models may exist. Derived from patient tumors without any genetic manipulation, they provide the assurance of primary cells with long-term reproducibility and scalability. Unlike traditional protocols for cell line creation, these cancer models eliminate the possibility of large scale cell line creation, these cancer models providing extremely high enzyme activity with more than 80 percent sequence coverage and robust stability. The Trypsin/MP/Gelatinase digestion protocol is modified by reductive methylation, making it extremely resistant to autolysis as shown in the spectrogam. It is chromatoaphically purified, yielding a highly pure active enzyme absent of other proteases. Each lot is tested by an end-point enzyme activity assay using mass spectrometry analysis and certified for use ensuring purity and performance consistency.

**Cayman Chemical**

www.caymanchem.com/cms/caymanchem/Literature/000171.pdf

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**New microplate-based method to measure OCR and ECA**

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**Irvine Scientific**

www.irvinescience.com/

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**Trypsin certified for MS**

**Biophoretics**

New Trypsin MS Approved is certified for mass spectrometry (MS), providing extremely high enzyme activity with more than 80 percent sequence coverage and robust stability. The Trypsin MS/Gelatinase digestion protocol is modified by reductive methylation, making it extremely resistant to autolysis as shown in the spectrogam. It is chromatoaphically purified, yielding a highly pure active enzyme absent of other proteases. Each lot is tested by an end-point enzyme activity assay using mass spectrometry analysis and certified for use ensuring purity and performance consistency.

**Biophoretics**

www.biophoretics.com

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**Comparing sensitivity and efficiency of N-Chip-seq and X-Chip-seq kits**

**Chromatrap**

Chromatrap has published a new article describing a genome-wide comparison of native and crosslinked chromatin immunoprecipitation followed by next-generation sequencing (ChIP-seq) using the company’s studying software component. The study compares the enrichment of the histone H3K4me3 modification across the whole genome, from chromatin prepared by both methods (native vs. cross link). The histone mark H3K4me3 was chosen for this study to highlight the sensitivity and efficiency of the Chromatrap spin column protocol for both native and cross-linked Chip-seq. Chromatrap. www.chromatrap.com/publications/

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**EntroGen releases BRCA Complete for targeted BRCA1/BRCA2 sequencing**

**EntroGen, Inc.**

BRCA Complete is a full solution for BRCA1/BRCA2 sequencing that includes reagents for target enrichment, library preparation and PCR cleanup in one package. The product comes with a user-friendly data interpretation software for reporting all clinically relevant somatic and germline mutations. This bioinformatics tool is fully customizable, providing users with complete control over the vast amount of data generated by NGS platforms. EntroGen also supplies sample and library quality control qPCR assays—DNA Fragmentation Quantification and Library Quantification for Illumina—to ensure reliable sequencing data output and efficient use of patient samples and sequencing reagents.

**EntroGen Inc.**

https://entrogen.com/web/
Abbott and Alere deal seems poised to move ahead

After months of wrangling over the merger, the pair agree to amend the terms of the deal.

BY JEFFREY BOULEY

ABBOTT PARK, Ill. & WALTHAM, Mass.—So, it looks like Abbott will be acquiring Alere Inc. after all. Unless, of course, something else changes to sour the mood in the wake of an amended deal announced in mid-April.

To catch you up, if you haven’t been following the story, Abbott in February 2016 confirmed a deal to acquire Alere for $56 per share. Just a little over a month later, Alere missed an extended deadline for its 10-K filing, though Abbott said it still projected that the merger would close by the end of 2016; however, in late April, Abbott CEO Miles White declined to comment as to whether the deal would close by the end of 2016; Abbott in mid-April. In November, Abbott sued Alere for violating deal terms. And then, in December of last year, Abbott said it wanted to terminate the deal, noting that Alere had lost significant value and was “not the company we agreed to buy.”

Even as early as March of this year, it seemed like the deal was dead in the water, with a Crain’s Chicago Business article noting that on top of everything else, other problems were cropping up at Alere, writing, “There seems to be no end of bad news at Alere, the diagnostic test maker that Abbott Laboratories is fighting desperately to avoid buying,” and pointing out specifically that Alere was looking into revenue-booking practices in its South Korean and Japanese locations, and “inappropriate conduct” at a South Korean subsidiary that may have involved the misallocation of between $5 million and $10 million of revenue between 2013 and 2016.

And yet, the two companies have come back to the table, announcing that as of April, they had agreed to amend the existing terms of their agreement for Abbott’s acquisition of Alere. Specifically, under the amended terms, Abbott will pay $53 per common share to acquire Alere, for a new expected equity value of approximately $5.5 billion, reduced from the originally expected equity value of approximately $4.8 billion.

The transaction is expected to close by the end of the third quarter of 2017, subject to the approval of Alere shareholders and the satisfaction of customary closing conditions, including applicable regulatory approvals.

Under the amended terms, the date by which necessary regulatory approvals must be received has been extended to Sept. 30, 2017, from April 30, 2017. Additionally, the companies have agreed to dismiss their respective lawsuits.

Although it has seemed eager for some time now to terminate its agreement to acquire Alere, Abbott has agreed to amend the deal and pay a little less for the company.

Canaccord Genuity diagnostics analyst Mark Massaro wrote in a note to investors, “We are positive, relieved and modestly surprised by the news that on Good Friday [that Abbott and Alere] agreed to amend their merger agreement … We believe the companies have approved anything at $50+ so we expect majority shareholder approval will not be a problem. The $51/share settlement bridged our prior thinking of a ‘price cut settlement’ of $48 … While we believe [the amendment] is fair to both parties, it still isn’t abundantly clear to us that Abbott wants to acquire Alere.”

And now, barring any new obstacles or legal wrangling, eyes will be looking toward the merged company and whether, amid all the questions, Alere—as a global leader in point-of-care diagnostics, will significantly expand Abbott’s global diagnostics presence and leadership and make the multi-billion-dollar deal worth the price and the stress it has brought. But regardless, the allure for Abbott (aside from possibly simply wanting to end legal proceedings) even with the financial questions is clear: Point-of-care testing is a fast-growing segment. It is becoming of importance to Abbott in the last half of 2016 as the company announced its acquisition of Alere.

Improving diabetes testing

BOSTON—Gestational diabetes mellitus (GDM), also known as diabetes in pregnancy, is a major cause of adverse pregnancy outcomes for both babies and mothers. Current standard-of-care testing for GDM screening and diagnosis is time-consuming, uncomfortable for the patients and reported to have poor reproducibility. But a research team at Brigham and Women’s Hospital, in collaboration with researchers from Harvard T.H. Chan School of Public Health, believe they may have a better way.

In the study, the investigators evaluated levels of the biomarker GCDS9 in plasma samples from 1,000 women undergoing routine screening and diagnosis of GDM and found that a single measurement of plasma GCDS9 any time between week 24 and week 28 of gestation identified women with GDM with high sensitivity and specificity. Compared to controls, the team reported that median levels of plasma GCDS9 were 8.5 times higher in women who failed a glucose challenge test and tenfold higher in women diagnosed with GDM.

Tesarox initiates program for anti-PD-1 antibody

WALTHAM, Mass.—Marking its first immuno-oncology candidate to enter a registration program, oncology-focused biopharma Tesaro Inc. announced in late April that following the recent identification of a fixed-dose and patient-centric dosing schedule, the ongoing clinical trial of TSR-042 has been expanded to enroll patients with metastatic microsatellite instability high endometrial cancer who have progressed following one or two prior chemotherapy treatments.

During the first 12 weeks of treatment, TSR-042 is administered once every three weeks, followed by a single dose administration every six weeks until disease progression. The intent of the study is to support a request for accelerated approval and Biologic’s License Application submission to the FDA. The primary endpoints of this trial are overall response rate and duration of response, and secondary endpoints include disease control rate, progression-free survival and overall survival.

“TSR-042 was the first antibody from our immuno-oncology portfolio to enter clinical trials, and following identification of a fixed-dose and patient-centric dosing schedule, we are pleased to be advancing TSR-042 into a registration program,” said Dr. Mary Lynne Hedley, president and chief operating officer of Tesaro. “With the recent approval of Zejula in the U.S., the initiation of this development program furthers our commitment to women with gynecologic tumors, including ovarian, fallopian tube and peritoneal cancer. We intend to continue our efforts with future combination studies of TSR-042 and Zejula.”

Zogenix completes enrollment for XZ008 Phase 3

EMERYVILLE, Calif.—Zogenix Inc., a pharmaceutical company developing therapies for the treatment of orphan and central nervous system disorders, recently announced that the last patient has been randomized into the treatment period of its first Phase 3 clinical trial evaluating XZ008 (low-dose fenfluramine) as an adjunctive treatment for seizures in children and young adults with Dravet syndrome.

The completion of patient randomization in Study 1 is an important milestone for our XZ008 Phase 3 development program in Dravet syndrome,” said Dr. Stephen J. Farr, president and CEO of Zogenix. “We look forward to the availability of top-line data from this study, which we expect in the third quarter of this year.”

Propranolol completes toxicity study for PRP

MELBOURNE, Australia—Propranolol, a beta-adrenergic blocking agent that has been used for the prevention of preterm labor, can be used to treat preeclampsia, pre-term labor, and intrauterine growth restriction. It is a beta-blocker that has been shown to be effective in the treatment of preterm labor, and it is a beta-blocker that is not associated with fetal bradycardia.

The study was conducted in a randomized, double-blind, placebo-controlled trial of 204 women with preterm labor who were randomized to receive propranolol or placebo. The primary endpoint of the study was the proportion of women who delivered within 7 days of randomization.

The results of the study showed that propranolol was statistically significantly more effective than placebo in reducing the risk of preterm delivery within 7 days of randomization. The median time to delivery was 4.5 days in the propranolol group and 8.0 days in the placebo group. The median time to delivery was 4.5 days in the propranolol group and 8.0 days in the placebo group.
Every one here

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